

Detecting Left Ventricular Impaired Relaxation using Moving Mesh Correspondences

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Abstract

This study presents a semi-automated assessment of the left ventricular (LV) *diastolic* function using anatomical cine cardiovascular magnetic resonance (CMR) imaging. Numerous clinical studies in echocardiography suggested that evaluating the diastolic function is essential in the assessment of many cardiovascular abnormalities including heart failure with preserved ejection fraction. However, most of the existing LV assessment algorithms based on CMR focus only on the *systolic* function, which essentially pertains to the analysis of global parameters such as ejection fraction or regional wall motion abnormalities. Anatomical cine CMR is widely used to assess the cardiac function because of its high soft tissue contrast. Unlike with transthoracic echocardiography (TTE), CMR is not limited by an acoustic window, and allows exhaustive myocardial imaging with excellent spatial resolution. The proposed method is based on three main steps: (1) non-rigid registration, which yields a sequence of endocardial boundary points over the cardiac cycle based on a user-provided contour on the first frame; (2) LV volume and filling rate computations over the cardiac cycle; and

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(3) automated detection of the peak values of early and late ventricular filling waves. We report comprehensive experimental evaluations over CMR data sets acquired from 47 subjects, including comparisons with independent reports for the same subjects from TTE. The proposed algorithm yielded a Cohen’s kappa measure of 0.70 and a Gwet’s AC1 coefficient of 0.70, a substantial agreement with the TTE results.

Keywords: cardiac left ventricle, diastolic function, image registration, image segmentation, magnetic resonance imaging.

1. Introduction

Most of the existing left ventricle (LV) assessment algorithms using cine cardiac magnetic resonance (CMR) focus on the *systolic function*, and are often limited to the analysis of regional wall motion abnormalities or the estimation of the ejection fraction [1, 2, 3]. However, the *diastolic function* is essential in the evaluation of various heart diseases, and several studies suggested that the assessment of the diastolic function is also important [4, 5, 6, 7]. Heart failure with a preserved left ventricular ejection fraction represents approximately 40%–50% of all cases of heart failure [7, 8], and is increasing in prevalence among the senior population [9]. Furthermore, a distinction between systolic and diastolic heart failure is essential, given the importance of the therapeutic and prognostic differences between these two subsets of heart failures [10]. Therefore, early and accurate diagnosis of abnormalities in diastolic filling is of the utmost importance.

Although direct measurement of the LV filling pressures is preferable, the use of angiography is not ideal for routine clinical assessments as several non-invasive methodologies have become widely available [11]. Currently, 2D echocardiography using flow Doppler imaging is widely used to measure transmitral velocities. The existing echocardiography studies are based on Doppler measurements at the tips of the mitral valve leaflets to determine peak velocities of mitral inflow [9], Doppler echocardiography to estimate the mitral flow and pulmonary ve-

22 nous flow [12, 13], and a color M-mode Doppler to estimate information such
23 as the ventricular relaxation or compliance from transmitral velocity profile,
24 among others. Despite these advances, transthoracic echocardiography (TTE)
25 has important disadvantages, including a limited field of view due to the acoustic
26 window, dependence on sample volume location, cosine θ errors relative to the
27 flow direction, and the inability to image approximately 15–20% of the patients
28 [5, 11].

29 Although multiphase computed tomography (CT) can also be used for the
30 analysis of the LV function, only a few studies were devoted to the analysis of
31 the diastolic function. Boogers *et al.* presented a comparison between CT and
32 2D echocardiography using tissue Doppler imaging, noting good correlations
33 for transmitral velocity, mitral septal tissue velocity, and estimation of the LV
34 filling pressures [14].

35 Alternatively, CMR imaging allows for an exhaustive myocardial evaluation
36 with high spatial resolution, and has several important advantages. They re-
37 lax the need for geometric assumptions and afford an excellent image quality.
38 Unlike CT, CMR involves no radiation exposure which allow population-based
39 screening and repeated scanning of the same patient. Some CMR studies relied
40 on phase contrast for the evaluation of the diastolic function [15, 16, 17, 18, 11].
41 In another study, a finite element based technique is used to estimate the dias-
42 tolic dysfunction using tagged CMR images [19]. However, these CMR acquisi-
43 tion protocols are not commonly used in routine clinical practices due to their
44 complex and time-consuming post processing and interpretation. Among other
45 magnetic resonance sequences, anatomical cine CMR remains the most widely
46 used sequence to assess the cardiac function [20]. Few notable exceptions that
47 used the anatomical cine MR to assess the diastolic function include Wu *et al.*
48 [21] who used long-axis views to compute mitral annulus sweep volume, and
49 Mendoza *et al.*[22] who used short-axis view to compute LV volumes and filling
50 rates. Analysis of the diastolic function using short-axis view of the anatomical

51 cine CMR requires delineation of LV from hundreds of images², making manual
52 segmentation impractical for standard clinical applications. Therefore, auto-
53 mated segmentation is important for the assessment of the diastolic function
54 [23].

55 This study proposes a method to assess the LV impaired relaxation using
56 short-axis cine CMR images. The proposed method consists of a semi-
57 automated LV segmentation approach and an automated detection of peak
58 values of early and late ventricular filling waves. Given a user-provided seg-
59 mentation of a single frame in a cardiac sequence, the proposed segmentation
60 approach delineates endocardial borders of the LV via point-to-point correspon-
61 dences. The moving mesh framework proposed in this study is fundamentally
62 different from previous approaches [24, 25]. Based on the concept of equivalent
63 volume elements of a compact Riemannian manifold [26] and yielding a unique
64 solution by solving a div-curl system, the proposed point-to-point approach pre-
65 vents mesh folding, i.e., grid lines of the same grid family will not cross each
66 other, an essential attribute in tracking cardiac tissues from a sequence of im-
67 ages.

68 We report comprehensive experimental evaluations over CMR data sets ac-
69 quired from 47 subjects, including comparisons with independent reports for the
70 same subjects from TTE. The proposed algorithm and TTE findings yielded a
71 Cohen’s kappa measure [27] of 0.70 and a Gwet’s AC1 coefficient [28] of 0.70.

72 2. Method

73 The proposed diastolic function analysis algorithm consists of *preprocessing*
74 and *detection of the E and A waves*, the early and late (atrial) ventricular filling
75 velocities, based on the computation of the LV filling rate curve. The proposed
76 approach allows for evaluating the diastolic function for all the patients who
77 undergo an CMR scan, including those who may not be primarily referred for

²Typically 200 images per subject

78 a diastolic function evaluation. The method is based on three main steps: (1)
 79 non-rigid registration, which yields a sequence of points over time, given a user-
 80 provided contour on the first frame; (2) computations of the LV filling rate and
 81 volume over the cardiac cycle; and (3) automatic detections of the maxima of
 82 the E and A waves.

83 2.1. Preprocessing

Given a user-provided segmentation of a single frame in a cardiac sequence, the proposed method segments endocardial borders of the LV via point-to-point correspondences (Refer to Fig. 1). We propose to use a moving mesh (or grid generation) framework [26] to compute point-to-point correspondences between the k^{th} image T_k and $(k+1)^{\text{th}}$ image T_{k+1} (for $k = 1, \dots, K-1$) defined over $\Omega \subset \mathbb{R}^2$ (K is the total number of frames in a cardiac cycle), thereby obtaining a sequence of points over time (Refer to Fig. 2). We state the problem as the optimization of a similarity/dissimilarity measure [29]:

$$\hat{\phi} = \arg \operatorname{opt}_{\phi} E_s(T_k, T_{k+1}, \phi(\xi)) \quad (1)$$

84 where $\xi \in \Omega$ denotes pixel location, $\phi : \Omega \rightarrow \Omega$ a transformation function and
 85 $E_s(\cdot)$ a measure of similarity. As this problem may not have a unique solution,
 86 we introduce in the following a deformation field using a monitor function μ and
 87 curl of end velocity field v , where $\mu : \Omega \rightarrow \mathbb{R}$ and $v : \Omega \rightarrow \mathbb{R}$.

88 2.1.1. Moving Mesh Generation

Let $\mu(\xi)$ be a continuous monitor function constrained by:

$$\int_{\Omega} \mu = |\Omega|. \quad (2)$$

The purpose of this step is to find a transformation $\phi : \Omega \rightarrow \Omega, \partial\Omega \rightarrow \partial\Omega$, so that

$$J_{\phi}(\xi) = \mu(\xi), \quad (3)$$

where J_ϕ denotes the Jacobian determinant of the transformation. The following computations yield a transformation ϕ , which verifies (3).

Step 1: Compute a vector field $\rho(\xi)$, which verifies

$$\operatorname{div} \rho(\xi) = \mu(\xi) - 1. \quad (4)$$

Step 2: Build a velocity vector field from $\rho(\xi)$:

$$\nu_t(\xi) = \frac{\rho(\xi)}{t + (1-t)\mu(\xi)}, \quad t \in [0, 1], \quad (5)$$

where t is an artificially introduced (algorithmic) time.

Step 3: Finally, ϕ is obtained by solving the following ODE:

$$\frac{d\psi(\xi, t)}{dt} = \nu_t(\psi(\xi, t)), \quad t \in [0, 1], \psi(\xi, t=0) = \xi, \quad (6)$$

89 and setting ϕ equal to ψ evaluated at $t = 1$: $\phi(\xi) = \psi(\xi, t = 1)$.

We add an additional constraint on the curl of $\rho(\xi)$ to (4). Then, we solve the ensuing div-curl system under the Dirichlet boundary condition to obtain a unique solution, as the above problem may have multiple solutions, i.e.,

$$\begin{cases} \operatorname{div} \rho(\xi) = \mu(\xi) - 1 & (7a) \\ \operatorname{curl} \rho(\xi) = v(\xi) & (7b) \end{cases}$$

90 with null boundary condition $\rho(\xi) = 0 \forall \xi \in \partial\Omega$, where $v(\xi)$ is a continuous
 91 function over Ω . Hence, the transformation can be fully parametrized by $J_\phi(\xi)$
 92 and $v(\xi)$. We ensure the uniqueness of the solution using the Dirichlet boundary
 93 condition [30]. The Dirichlet boundary conditions may cause the motion errors
 94 to be higher at the image boundaries, and therefore, we pad both images by
 95 zeros.

96 With the above parametrization, we reformulate (1) as the following con-
 97 strained optimization problem:

Problem: Given two images T_k and T_{k+1} , defined over Ω , find a function

pair $\{\mu(\xi), v(\xi)\}$ that optimizes cost (1) s.t.:

$$\begin{cases} \int_{\Omega} \mu(\xi) d\xi = |\Omega| & (8a) \\ \tau_h > \mu(\xi) > \tau_l, \quad \xi \in \Omega' \subset \Omega & (8b) \end{cases}$$

98 where $0 < \tau_l$ ensuring that $\phi_{\mu, v}$ is a diffeomorphism, and Ω' is a sub-region of
 99 image domain Ω .

100 Constraint (8a) ensures that the areas of the domain and co-domain are equal
 101 after transformation, and constraint (8b) limits the amount of compressibility,
 102 which is controlled by parameters τ_l and τ_h , within sub-region Ω' . Note that a
 103 diffeomorphism corresponds to a positive transformation Jacobian determinant,
 104 which is enforced explicitly via the monitor function [26].

105 The above problem can be solved by a *step-then-correct* optimization strat-
 106 egy. We compute a sequence of corresponding points on the endocardial border
 107 in all the frames of a cardiac sequence using transformation function $\hat{\phi}$, given
 108 the segmentation on the first frame.

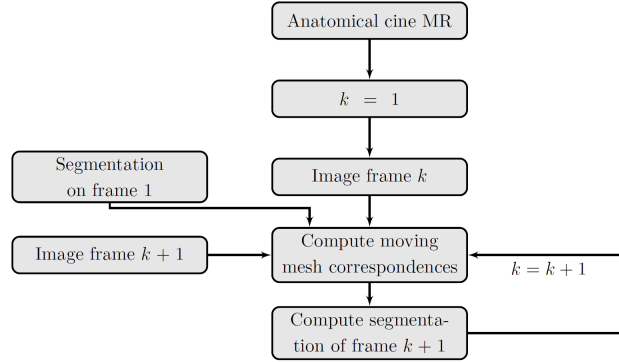


Figure 1: The proposed semi-automated delineation of the left ventricle

109 2.2. Detection of E and A waves

110 In order to detect the E and A waves, we need to compute the LV filling
 111 rate. The computation of the LV filling rate measurements is based on several
 112 processing steps. First, the LV volumes $\{V_k\}$ were computed for all k in the

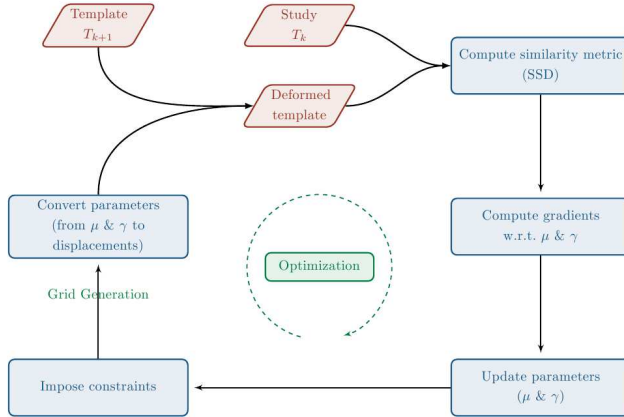


Figure 2: Computation of moving mesh correspondences

113 cardiac cycle, where V_k denotes the LV volume at k^{th} cardiac phase. For each
 114 cardiac phase, the contours for the LV cavities were automatically identified
 115 using the registration step above, given manual contours on the first frame.
 116 The papillary muscles were regarded as part of the LV cavity and were included
 117 in the LV volume computation. We used the short-axis image sequences that
 118 contain the LV cavity, and applied the Simpson's rule as well as the LV areas
 119 and slice spacing in computing volume V_k . This give us V_k as a function of time
 120 step k (Refer to Fig. 3(a) and (c)). We further compute the first derivative
 121 of the LV volumes with respect to time, thereby obtaining the LV filling rate
 122 dV_k/dt (Refer to Fig. 3(b) and (d)).

123 E and A are the early and late (atrial) ventricular filling velocities, which
 124 can be computed using the LV filling rate. In normal subjects, the LV inflow
 125 velocity is at its highest point during early diastole (E wave), with a smaller
 126 LA contraction (A wave), which results in $E/A > 1$. In patients with impaired
 127 relaxation, the LV pressure rises at early diastole, which yields a decrease in
 128 the E wave. Furthermore, the left atrium contraction highly contributes to the
 129 LV filling, which yields an increase in the A wave. Therefore, the impaired
 130 relaxation yields $E/A < 1$.

131 In order to detect the peak values of the E and A waves, we first identify

132 all the local maxima of the LV filling rate curve based on a first derivative test.
 133 Then, we select the highest and second highest local maxima. The start of
 134 the diastolic phase is identified by detecting the time at which V_k is minimum.
 135 Among the two maxima, we take the one closer to the start of the diastolic
 136 phase as the E wave, and the other one as the A wave.

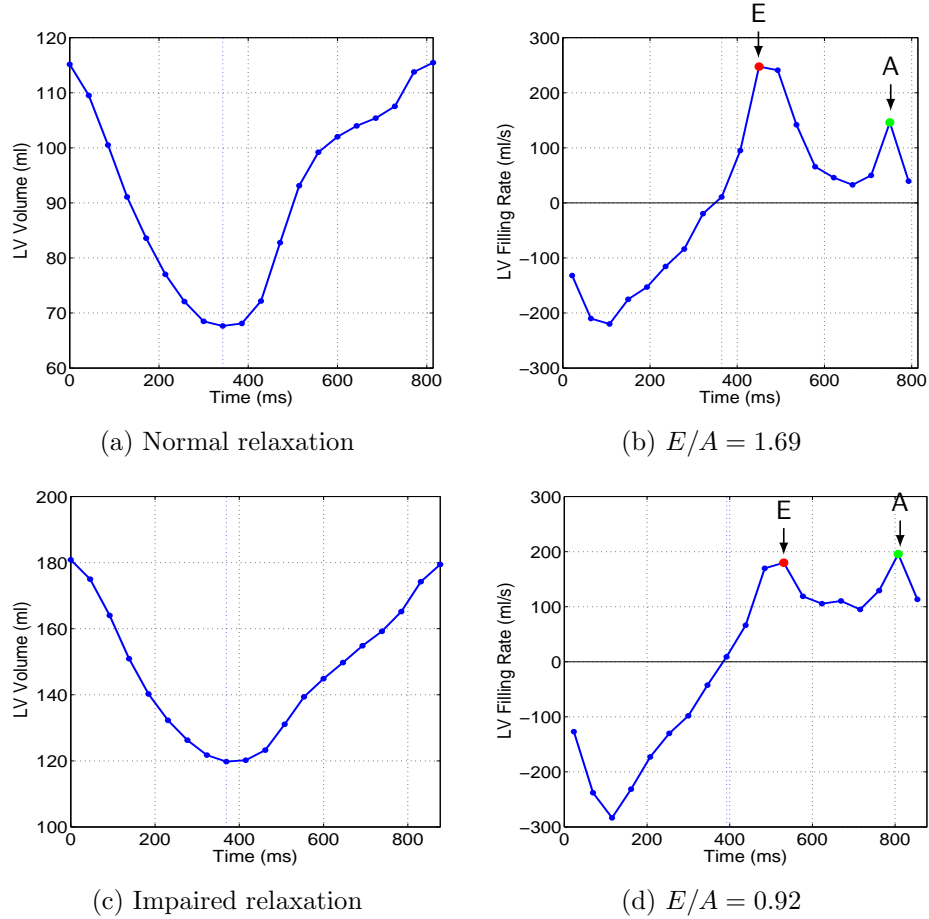


Figure 3: LV volume vs. time curves for: (a) typical normal relaxation; (b) typical impaired relaxation. Corresponding LV filling rate (dV_k/dt) curves are given by (c) and (d). The proposed method used LV volume curve to identify the start of the diastolic phase, and automatically detect the maximum values of E and A waves.

137 **3. Experiments**

138 Fifty three patients (out of 100 patients collected retrospectively as a part of
139 computer assisted image based cardiac disease diagnosis and monitoring study)
140 who had undergone cardiac CMR and TTE with tissue Doppler imaging between
141 2007 and 2011 at London Health Sciences Centre University Hospital and St.
142 Joseph’s Hospital, London, Canada were included in the study. Inclusion criteria
143 were: (1) the time difference between CMR and TTE exams is less than one year;
144 and (2) TTE assessments included the peak early and late ventricular filling
145 velocity values. Six patients were removed since the time differences between
146 MR and TTE studies were more than one year. No patients were excluded
147 based on CMR image quality or post-processing results. The mean and standard
148 deviation of the time difference between the CMR and TTE exams for the 47
149 subjects included in the study is 1.7 ± 2.6 months. All patients participating
150 in this study had a clinical indication for cardiac MRI. The indications were
151 ischemia (13), valve disease (2), cardiomyopathy (7), myopericarditis (3), with
152 the remainder of patients not having indications recorded. Although 9 patients
153 were found to have global systolic dysfunction and 8 patients were found to
154 have regional systolic abnormalities on MRI, a history of systolic dysfunction
155 was provided in only one patient prior to MRI scanning. There were no healthy
156 volunteers.

157 The short-axis CMR image datasets consist of 20 – 25 functional 2D images
158 per cardiac cycle. The CMR data were acquired on 1.5T CMR scanners with
159 fast imaging employing steady state acquisition (FIESTA) mode. The data
160 consists of images from 31 male and 16 female subjects, and the average age of
161 subjects is 51.6 ± 16.7 years. The details of the datasets are presented in Table
162 [1](#).

163 The size of the grid was selected automatically based on a bounding box
164 containing the initial segmentation drawn on the first frame. A margin of 10
165 pixels around the bounding box was added to allow deformations outside the
166 bounding box. For the step-then-correct algorithm, we set the threshold for

167 the step-size to 0.01 and the maximum number of iterations to 25. The initial
 168 value of the step-size and the factor to reduce step-size were set to 0.5 and 2/3,
 169 respectively. Given the high variability in left ventricular motion, the following
 170 parameter values were used for all cases so to allow large tissue deformations:
 171 $\tau_h = 4$ and $\tau_l = 0.1$.

Table 1: Details of the datasets used in evaluation of the proposed method.

Description	Value
Number of patients	47
Patient age (mean \pm std)	51.6 ± 16.7 years
Patient age range	16 — 79 years
Sex, m/f	31/16
Short-axis image size	(144×192) — (512×512) pixels
Number of frames (K)	20 — 25
Pixel spacing	(0.68×0.68) — (1.88×1.88) mm
Slice thickness	8 — 10 mm

172 In Fig. 4, we give a representative sample of the segmentation results for
 173 apical, mid-cavity and basal frames.

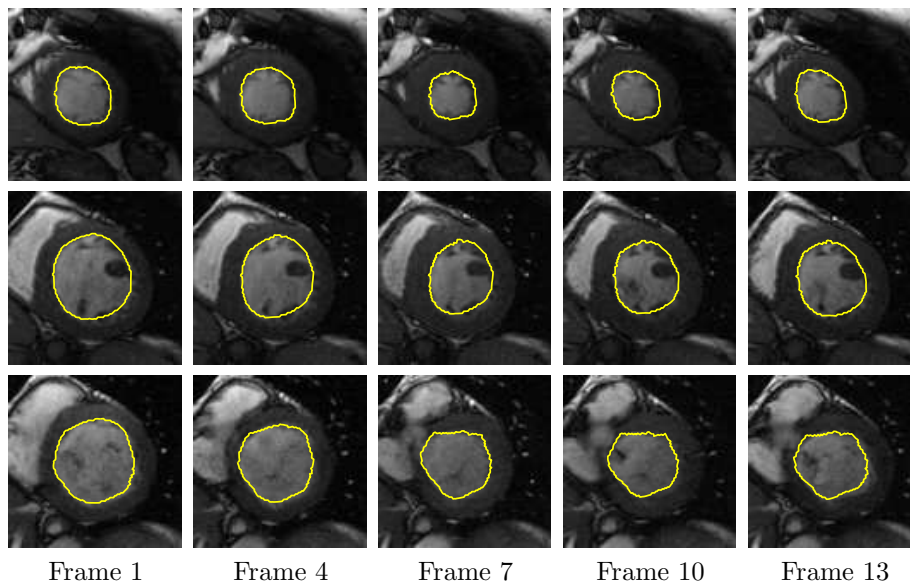


Figure 4: Representative examples of the LV boundary tracking using the proposed method: apical(1st row), mid-cavity (2nd row) and basal (3rd row) frames.

174 Table 2 shows the parameters estimated using the proposed method. The
 175 parameters include ejection fraction (EF), End-diastolic volume (EDV), End-
 176 systolic volume (ESV) and stroke volume (SV). The table also reports mitral
 177 deceleration time which was computed using the LV filling rate for each subject.

Table 2: Details of the global parameters computed using the proposed method.

Description	Value	Range
End-diastolic volume (ml)	121.4 ± 50.7	38.8 — 242.9
End-systolic volume (ml)	80.3 ± 47.1	18.1 — 205.3
Stroke volume (ml)	41.1 ± 14.9	20.6 — 83.5
Ejection fraction (%)	37 ± 13	13 — 61
Mitral deceleration time (ms)	141.1 ± 52.3	25.5 — 257.3

178 Comparisons between the proposed method and TTE reports on diastolic
 179 function are given in Table 3. The following criteria was used for the clas-
 180 sification: $E/A < 1$ corresponds to impaired relaxation; and $E/A \geq 1$ cor-
 181 responds to normal, pseudonormal or Type 3 relaxation [5]. The proposed
 182 method and TTE findings agree that 18 and 22 subjects have impaired and
 183 normal/pseudonormal/Type 3 relaxations, respectively.

Table 3: Detecting impaired relaxation in LV diastolic function using the proposed method and TTE. The following criteria was used for the classification: $E/A < 1$ corresponds to impaired relaxation; and $E/A \geq 1$ corresponds to normal, pseudonormal or Type 3 relaxation [5].

	TTE		
	Impaired Relaxation	Normal, Pseudonormal or Type 3 Relaxation	Total
Cine CMR			
Impaired Relaxation	18	1	19
Normal, Pseudonormal, Type 3 Relaxation	6	22	28
Total	24	23	47

184 *3.1. Cohen's Kappa*

We computed the Cohen's kappa coefficient between the proposed method and TTE findings as follows.

$$\kappa = \frac{Pr(a) - Pr(e)}{1 - Pr(e)} \quad (9)$$

The observed percentage agreement $Pr(a)$ is given by

$$Pr(a) = \frac{A + D}{N} \quad (10)$$

where A , D and N denote the number of times both methods classify a subject into impaired relaxation, the number of times both methods classify a subject into normal relaxation, and total number of subjects, respectively. The overall probability of random agreement $Pr(e)$ is given by

$$Pr(e) = \left(\frac{A1}{N} \times \frac{B1}{N} \right) + \left(\frac{A2}{N} \times \frac{B2}{N} \right) \quad (11)$$

185 where $A1 = A + C$, $A2 = B + D$, $B1 = A + B$, and $B2 = C + D$. B denotes
 186 the number of subjects classified into normal relaxation by CMR and impaired
 187 relaxation by TTE, and C vice versa.

188 The proposed method and TTE findings yielded a Cohen's Kappa coefficient
 189 of 0.70, a substantial agreement[31].

190 *3.2. Gwet's AC1*

Gwet's AC1 is computed by [28]:

$$AC1 = \frac{Pr(a) - e(\gamma)}{1 - e(\gamma)} \quad (12)$$

where

$$e(\gamma) = 2P_1(1 - P_1) \quad (13)$$

The approximate chance that a method (TTE or CMR) classifies a subject into impaired relaxation P_1 is given by

$$P_1 = \frac{A1 + B1}{2N} \quad (14)$$

191 The proposed method and TTE findings yielded a Gwet’s AC1 coefficient of
192 0.70.

193 3.3. Reproducibility

194 Inter-observer and intra-observer variabilities were measured over a data set
195 of 10 subjects. Two independent readers, blinded to TTE and each other’s
196 contours, traced the manual endocardial contours on the first frame. Intra-
197 observer variability was evaluated based on one of the readers. Table 4 reports
198 the inter-observer and intra-observer variabilities in terms of Intra Class Corre-
199 lation (ICC), Bland-Altman test, and Pearson correlation coefficient (R). The
200 parameters estimated using the proposed approach demonstrated good consis-
201 tency in terms of ICC and Pearson correlation coefficient.

Table 4: Reproducibility of CMR diastolic function measurements.

	Intra-observer (cases = 10)			Inter-observer (cases = 10)		
	ICC (95% CI)	Bias (Limits of agreement)	R	ICC (95% CI)	Bias (Limits of agreement)	R
E (1/s)	1.00 (1.00, 1.00)	0.00 (-0.08, 0.08)	1.00	1.00 (0.99, 1.00)	0.019 (-0.470, 0.508)	0.99
A (1/s)	1.00 (1.00, 1.00)	0.02 (-0.06, 0.11)	1.00	0.97 (0.89, 0.99)	0.635 (-0.480, 1.751)	0.98
E/A	1.00 (1.00, 1.00)	-0.01 (-0.05, 0.03)	1.00	0.96 (0.84, 0.99)	-0.24 (-0.73, 0.26)	0.99
MDT (ms)	0.84 (0.48, 0.96)	-16.6 (-90.5, 57.3)	0.89	0.83 (0.46, 0.96)	3.9 (-61.9, 69.7)	0.84

202 4. Discussion

203 An important advantage of our semi-automated method is that it signifi-
204 cantly reduces the amount of time required for segmenting the left ventricle.

205 This allows the user to analyse the function over the entire cardiac cycle in ad-
206 dition to the computation of common clinical measures such as ejection fraction
207 or stroke volume. Our algorithm has the following advantages over prior LV
208 segmentation works: (1) it removes the need for a time-consuming, manually-
209 built training set; (2) it does not make prior assumptions as to the distributions
210 of intensity and shape.

211 The proposed method relied on short-axis MR images to analyse the diastolic
212 function which differs from the method proposed by Wu *et al.* using two-, three-
213 , and four-chamber views of the cine MR sequences [21]. The method proposed
214 by Wu *et al.* relied on the mitral annulus sweep volume to analyse the diastolic
215 function and used only six points to estimate the mitral annulus using spline
216 interpolation, whereas the proposed method relied on several points (around
217 30 points per segmentation) from about 10 short-axis slices to estimate the
218 volume of the LV. Further, the method proposed by Wu *et al.* required manual
219 correction of atrioventricular junction tracking of about 30% of the cases whereas
220 no manual correction was employed for the proposed method. However, one of
221 the disadvantages of using only the short-axis is that it is hard to include the
222 effects of shortening of the heart along the long-axis. We are planning to address
223 this problem by the fusing the information from long-axis slices in the future.

224 In contrast to the automated methods in [22] and [23], the proposed segmen-
225 tation approach does not rely on intensity threshold for image segmentation. A
226 major drawback of threshold-based segmentation approaches is that they of-
227 fer a limited framework for strong prior incorporation [32], and often require a
228 manual correction of the segmentation results. For example, 52% of the study
229 population in [23] required manual correction of the LV contours. Segmentation
230 of the LV is acknowledged as a challenging problem, and therefore, incorpo-
231 ration of prior knowledge is essential to increase the robustness and accuracy.
232 The proposed approach allows for the incorporation of a strong prior, a user
233 defined contour of the LV on the first frame. The method has been shown to
234 be robust, and yielded accurate segmentation results in comparison to manually
235 drawn contours for both left and right ventricles under various heart conditions

236 [3, 29, 33]. Further, the proposed method demonstrated good consistency in
237 reproducing similar results for inter-observer and intra-observer experiments.

238 The proposed method relies on the LV volume curves to compute the LV
239 filling rates, and the early and late fillings are expressed in millilitres per second.
240 These measurements are different from the TTE findings which measure the
241 velocity of the blood flow through the mitral valve in centimetres per second.
242 The peak values of the early and late filling ratios for velocity and flow will
243 be the same only if the size of the mitral valve does not change during the
244 diastolic phase. As well, the proposed method ignores the effect of mitral valve
245 regurgitation when computing the early and late filling rates.

246 Another important MR measurement that can be used for the diagnosis of
247 diastolic dysfunction is the phase contrast velocity measurement at the mitral
248 valve. However, our data set was acquired retrospectively from the standard
249 clinical scans, and therefore, only a small amount of subjects (8 out of 47)
250 had a phase contrast velocity scan at the mitral valve. As a future study, we
251 are planning to compare the proposed methods against the mitral valve flow
252 measurements with a larger data set.

253 **5. Limitations of the proposed study**

254 One of the limitations of our method is that it requires manual contouring
255 of one time frame for a given slice position. Although more time-consuming
256 than automated methods, the proposed method allows for greater accuracy
257 throughout the remainder of the cardiac cycle.

258 The study analysed the CMR and TTE data retrospectively and none of
259 the patients had both exams on the same day. Although the maximum time
260 difference between MR and TTE exams was one year, it might have resulted
261 in changes in cardiac function for some of the subjects. This could be one of
262 the reasons for the difference in diastolic function estimated by the proposed
263 method and TTE findings.

264 We considered TTE exams as the reference standard to assess the perfor-

265 mance of the proposed method since invasive hemodynamic procedures are not
266 used in standard clinical practice. TTE exams remain the generally accepted
267 non-invasive reference method for diastolic function assessment [21]. The study
268 did not also have the follow-up data to assess the prognostic significance of the
269 proposed method.

270 The algorithm was tested over a dataset of only 47 subjects. However, the
271 proposed algorithm will allow testing over a larger data set since it only requires
272 minimal user input.

273 The LV volumes are computed based on short-axis slices of the MRI with
274 8–10 mm slice thickness, which might have impacted the volumetric assessment.
275 The proposed analysis based on short-axis images also ignores the descent of
276 the mitral valve through the short-axis plane during systole and ascent during
277 diastole. In the future, we are planning to address these problems by tracking
278 the mitral valve over the cardiac cycle using long-axis cine MR sequences.

279 **6. Conclusions**

280 In this study, we proposed a semi-automated approach to estimate the left
281 ventricular (LV) diastolic function parameters using anatomical cine cardiac
282 magnetic resonance (CMR) imaging. Our method uses with a diffeomorphic
283 nonrigid registration to obtain a sequence of points over time, given a manual
284 contour on the first frame. Then, it computes the LV volume and filling rate
285 over the entire cardiac cycle. Finally, it automatically detects the peak values of
286 the E and A waves using the LV filling rate contour, thereby classifying the dias-
287 tolic function into two categories: normal/pseudonormal/Type 3 and impaired.
288 We performed experimental evaluations over CMR data sets acquired from 47
289 subjects, including comparisons with independent reports for the same subjects
290 from TTE. The proposed method correlated well with TTE, and yielded a Co-
291 hen’s kappa measure of 0.70 and a Gwet’s AC1 coefficient of 0.70, a substantial
292 agreement with the TTE results. The diastolic function parameters estimated
293 using the proposed approach also demonstrated good consistency in terms of

294 Intra Class Correlation (ICC), Bland-Altman test, and Pearson correlation co-
295 efficient.

296 **Conflicts of Interest**

297 None declared.

298 **Ethical Approval**

299 The study was approved by the University of Western Ontario Research
300 Ethics Board.

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303 **References**

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