A framework to measure myocardial extracellular volume fraction using dual-phase low dose CT images

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Purpose: Myocardial extracellular volume fraction (ECVF) is a surrogate imaging biomarker of diffuse myocardial fibrosis, a hallmark of pathologic ventricular remodeling. Low dose cardiac CT is emerging as a promising modality to detect diffuse interstitial myocardial fibrosis due to its fast acquisition and low radiation; however, the insufficient contrast in the low dose CT images poses great challenge to measure ECVF from the image.

Methods: To deal with this difficulty, the authors present a complete ECVF measurement framework including a point-guided myocardial modeling, a deformable model-based myocardium segmentation, nonrigid registration of pre- and post-CT, and ECVF calculation.

Results: The proposed method was evaluated on 20 patients by two observers. Compared to the manually delineated reference segmentations, the accuracy of our segmentation in terms of true positive volume fraction (TPVF), false positive volume fraction (FPVF), and average surface distance (ASD), were $92.18\% \pm 3.52\%$, $0.31\% \pm 0.10\%$, 0.69 ± 0.14 mm, respectively. The interobserver variability measured by concordance correlation coefficient regarding TPVF, FPVF, and ASD were 0.95, 0.90, 0.94, respectively, demonstrating excellent agreement. Bland-Altman method showed 95% limits of agreement between ECVF at CT and ECVF at MR.

Conclusions: The proposed framework demonstrates its efficiency, accuracy, and noninvasiveness in ECVF measurement and dramatically advances the ECVF at cardiac CT toward its clinical use.

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Key words: extracellular volume fraction, low dose, cardiac CT, deformable model, modeling

1. INTRODUCTION

For a variety of cardiomyopathies and heart failure, diffuse myocardial fibrosis (DMF) has been identified as a common disease process. Both animal and human studies demonstrated that DMF was associated with reduced ventricular function, abnormal cardiac remodeling, and increased passive stiffness. Myocardial tissue composition can be noninvasively investigated by measuring the T1 time of the myocardium, termed T1 mapping.¹⁻³ Myocardial extracellular volume fraction (ECVF), an imaging biomarker of expanded extravascular extracellular space, can be derived from the T1 values of myocardium and blood pool. ECVF is highly associated with

diffuse myocardial fibrosis, a hallmark of pathologic ventricular remodeling.⁴

Elevated cardiac MR ECVF has been observed in multiple conditions, including heart failure secondary to ischemic and nonischemic cardiomyopathies, aortic valve disease, and hypertrophic cardiomyopathy.⁵⁻⁹ Cardiac MR ECVF application was limited by both logistical and technical challenges. Cardiac MR is contraindicated in patients with cardiac implants and ECVF quantification requires a research T1 mapping sequence, which is currently only available in a handful of academic institutions. MOLLI T1 mapping sequence also has some heart rate dependence, which may bias results in patient with fast heart rate. DMF is a global process and 3D

FIG. 1. Poor quality of low dose postcontrast cardiac CT images. The first two images are axial slices of two patients, and the last two are reformatted short axis slices of the other two patients. All images are shown with standard soft tissue window/level: [450, 50].

whole heart ECVF quantification is highly desirable from a clinical point of view. However, 3D ECVF coverage is difficult to achieve in cardiac MR due to the 2D breath hold acquisition technique. Compared with cardiac MR, cardiac CT is widely available, and a whole heart 3D acquisition could be finished in a single heartbeat with the state-of-the-art 320 slice MDCT scanners. Cardiac CT ECVF quantification opened the possibility of evaluating myocardial physiology beyond structure changes during a coronary angiography exam with acceptable radiation and contrast exposure. Therefore, we sought to use a dual-phase cardiac CT to determine ECVF and demonstrated the successful substitution of cardiac CT for cardiac MR in ECVF analysis in our previous work.¹⁰ However, the low contrast sensitivity and poor quality of the low dose CT images pose a significant challenge in integrating this novel technique into the clinic practice.

In this paper, we developed a framework for quantification of cardiac CT ECVF using dual-phase low dose CT data and provided a toolkit for ease of use by clinicians. This method provides accurate pixelwise ECVF calculation, which makes both global and regional ECVF quantification possible. 3D surface and 17 segments polar plot accommodate easy visualization of the abnormalities.

Myocardium segmentation is an indispensable component of ECVF calculation. Jolly *et al.*¹¹ provided a method to automatically extract the myocardium by first a global localization of the left ventricle and then a region based expectation and maximization segmentation. Chen *et al.*¹² presented a hybrid method by integrating the shape prior information with the graph cut (GC) method. A pseudo-3D strategy was applied for the initialization based on the live wire (LW) method, and then the shape information generated from the initialization step was integrated into a GC cost function. Ecabert *et al.*¹³ presented a model-based approach for the whole heart segmentation. First, pose misalignment was corrected by matching the model to the image using a global similarity transformation, and then the model was deformed to match the boundaries of the patient's anatomy.

The poor quality of low dose cardiac CT images poses a big challenge to the segmentation as shown in Fig. 1. Shape constraints is valuable in improving the accuracy of the segmentation, especially in the region where no strong edges exist; however, due to the large variation of the myocardial shape, aligning an established shape atlas with the patient image is not robust, which motivates us to develop a patient spe-

cific myocardial model based on a sparse point set. Unlike the modeling method provided in Ref. 14, where an initial regular Ellipsoid is fitted to the 3D guided-points by minimizing an error function consisting of the sum of a smoothing term and a point matching term, we present a Bézier contour^{15,16} based modeling method. This modeling method does not need to deform an initial model, therefore avoiding the deterioration of the element quality. This model is not only used in a deformable model-based segmentation method, but also used to produce a 17-segments model according to the American Heart Association (AHA) guideline.²¹

Along with the model, a deformable model-based segmentation method is developed. This method incorporates both region information and shape constraints into one energy function, which drives the initial model, provided by the modeling method, toward the myocardial boundary. All the functionalities are incorporated into one ECVF toolkit (ECVTK) to facilitate ECVF measurement.

The novelties of this paper lie in the ECVF framework and its novel components including point-guided modeling, deformable model-based segmentation and the derivation of ECVF using dual-phase CT, which is first proposed by our group.

2. METHOD

In this section, we first present the principle of ECVF calculation using dual-phase CT, and then describe the entire framework of ECVF calculation followed by the detail of each component of the framework.

2.A. Principle of ECVF calculation using dual-phase CT images

An experimental ECVF calculation equation has been proposed in our previous work,¹⁰ but the principle behind the ECVF calculation has not been elucidated so far. In this section, we present the derivation of the ECVF calculation equation based on the tissue compartmental model.

A tissue is considered to be made of three well-defined regions (see Fig. 2): (1) a vascular space through which the blood flows; (2) an extravascular extracellular space (EES) which provides the support structure of the tissue; and (3) the cellular space.

Iodine contrast agent in a target organ or blood plasma causes greater absorption and scattering of x-ray radiation,

FIG. 2. Iodinated contrast medium distribution in a three-compartment physiology model. (Left) a typical CT image with a ROI denoted by a bounding box. (Middle) one pixel within the ROI. (Right) three-compartment physiology model of the pixel: cell space, capillary space, and extravascular extracellular space (EES). The stars represent the iodinated contrast molecules constrained within the capillary space and the EES.

which results in an increase in CT attenuation and contrast medium enhancement in the CT image. For a given voltage, the proportionality of contrast enhancement to iodine concentration is near constant.¹⁷ Iodinated contrast media consist of relatively small molecules (molecular weight, 800–1600) that are highly diffusible. Intravascular contrast media are distributed rapidly and extensively outside the blood vessels in volumes approaching that of the extracellular space, i.e., extravascular extracellular space plus capillary space, after injection.^{18,19}

Before the derivation of the ECVF calculation equation, we define the following parameters, v_p : volume of the vascular space, v_c : volume of the cellular space, v_{EES} : volume of the EES, v_{ECV} : volume of the vascular space plus EES, i.e., $v_p + v_{EES}$, v_{tissue} : volume of the tissue space, i.e., $v_{ECV} + v_c$, c_{ECV} : contrast media concentration within extracellular space, c_{tissue} : contrast media concentration within the tissue.

Because the Hounsfield Unit (HU) enhancement of CT is proportional to the iodine contrast concentration of the tissue within one voxel (not the concentration in ECV), for one voxel within the myocardium, we have

$$HU_{\text{postmyocardium}} - HU_{\text{premyocardium}} = k \times c_{tissue}, \quad (1)$$

where $HU_{\text{postmyocardium}}$ and $HU_{\text{premyocardium}}$ are the HU of the voxel of the myocardium in the postcontrast and precontrast CT, respectively. k is a constant. According to mass conservation,

$$\begin{aligned} c_{tissue} \times v_{tissue} &= c_{ECV} \times v_{ECV} \Rightarrow c_{tissue} = \frac{v_{ECV}}{v_{tissue}} \times c_{ECV} \\ &= ECV \times c_{ECV}, \end{aligned} \quad (2)$$

where ECVF is the ratio of the volume of extracellular space and the volume of the tissue space. Replace c_{tissue} in Eq. (1) with (2),

$$HU_{\text{postmyocardium}} - HU_{\text{premyocardium}} = k \times ECV \times c_{ECV}. \quad (3)$$

Directly using Eq. (3) to calculate ECVF of the myocardium encounters the trouble that both k and c_{ECV} are unknown. We take the voxel of the blood pool as the reference since we know the ECVF of the blood pool is $1.0 - \text{Hct}_{\text{blood}}$, where the hematocrit $\text{Hct}_{\text{blood}}$, is the volume percentage (%) of red blood cells in blood, which varies from patient to patient, but can be measured by the blood sample. Apply Eq. (3) on the voxel of the blood pool with the assumption

that iodine contrast agent reaches dynamic equilibrium between myocardium and blood pool,

$$\begin{aligned} HU_{\text{postbloodpool}} - HU_{\text{prebloodpool}} \\ = k \times (1.0 - \text{Hct}_{\text{blood}}) \times c_{ECV}. \end{aligned} \quad (4)$$

Divide Eq. (3) by (4),

$$\begin{aligned} \text{ECVF} &= \frac{HU_{\text{postmyocardium}} - HU_{\text{premyocardium}}}{HU_{\text{postbloodpool}} - HU_{\text{prebloodpool}}} \\ &\quad \times (1.0 - \text{Hct}_{\text{blood}}). \end{aligned} \quad (5)$$

The voxel of the blood pool is used as the reference. To alleviate the influence of the noise, we use the average HU enhancement of the blood pool.

2.B. ECVF measurement framework

Figure 3 shows the framework to measure ECVF using dual-phase low dose cardiac CT images. The framework takes pre- and postcontrast CT as inputs and outputs ECVF map, ECVF 17-segments model,²¹ ECVF global model, and ECVF statistics report. This framework consists of four main components. The point-guided modeling component produces an initial myocardial model based on a few anatomical points selected in the postcontrast CT image by the clinician. This model has twofold purposes: an initial segmentation for the subsequent deformable model-based segmentation and 17-segments model generation for ECVF statistics. The deformable model-based segmentation component drives the initial model toward the myocardial surface to refine the segmentation. ECVF calculation is a pixelwise operation as shown in Eq. (5), which requires the alignment between the pre- and postcontrast CT using the nonrigid registration component. After registration, the segmentation result, represented by a 3D surface mesh, the postcontrast CT and the aligned precontrast CT are input into the ECVF calculation component to produce ECVF map, ECVF 17-segments model, ECVF global model, and ECVF statistics report. All these components are integrated into an ECVTK.²⁰ In Secs. 2.C–2.G, we present details for each component.

2.C. Point-guided myocardial modeling

Using a few points selected by clinicians to create a patient-specific model is helpful in providing an initial

FIG. 3. ECVF measurement framework using dual-phase low dose cardiac CT images. The inputs are pre- and postcontrast CT and the outputs are ECVF map, ECVF 17-segments model, ECVF global model, and statistics report. Four components: point-guided modeling, deformable model-based segmentation, nonrigid registration, and ECVF calculation are integrated into one ECVTK.

estimation and imposing shape constraints for model-based segmentation. The basic idea to build the myocardium model is to use clinician specified points to create interlaced Bézier contours^{15,16} along both longitude and latitude directions. The intersection points of these Bézier contours are first connected to constitute quadrilateral and triangular elements, and then each quadrilateral element is further divided into two triangles to produce a triangular mesh. This procedure is performed on both endocardium (endo) and epicardium (epi) to produce endo and epi surface models, and then these two meshes are combined into one closed myocardial surface model. Figure 4(a) shows the flowchart of this method with main components illustrated in Fig. 4(b). The flowchart includes six steps:

- (1) Both endo and epi surface meshes begin from a few points selected by a clinician. In addition to the apex, the other points are selected in the basal, middle, and apical short axis slices (see Fig. 5) as suggested by AHA standard myocardial segmentation.²¹ There is no stringent requirement for selecting the points within the slice. Roughly evenly spaced four or five points are acceptable if we do not consider the segmentation of papillary muscles. There are two special points for the building of the 17-segments model. Please see Sec. 2.F for details. It takes about 1 min to select the points on average.
- (2) Next, a Bézier curve is fitted on each of the basal, middle, and apical slices as shown in Fig. 4(b) (along with one apex point), for the following automatic myocardial modeling.

FIG. 4. Myocardial modeling. (a) modeling flowchart. (b) modeling illustration. Four epi points are selected in the basal short axis slice to produce Bézier contours. The Bézier contours and the apex are used to produce longitudinal grid and interlaced grid. The epi and endo models are connected at the bottom to produce a closed model.

FIG. 5. Segments along Vertical Long Axis (VLA) (2 Chamber). Four segments: basal (tips of the mitral valve leaflets), midcavity (papillary muscles), apical (beyond papillary muscles but before cavity ends), and apex segments. Reproduced by permission from American Heart Association, *Circulation* 105(4), 539–542 (2002). Copyright 2002.

- (3) Produce longitude Bézier contours. Each contour is resampled along the longitude direction. The number of resampled points is determined by the parameter: *longitude resolution*. These resampled points are used to produce longitude Bézier contours intersected at the apex as shown in Fig. 4(b).
- (4) The longitude Bézier contours are resampled along the latitude direction with specified *latitude resolution*, and Bézier fitting is performed to produce latitude Bézier contours.
- (5) The intersection points of the interlaced Bézier contours are connected to produce quadrilateral elements if there is no apex in four neighboring points, otherwise producing triangular elements. For each quadrilateral element, it is further divided into two connected triangles, leading to a triangular surface mesh as shown in Fig. 4(b).
- (6) The above procedures are performed on both endo and epi to produce two triangular surface meshes. The vertices located in the basal planes of the two meshes are connected to produce the final closed myocardium surface model.

The proposed modeling technique is robust and easy to be implemented because the basic operation involved in the modeling is Bézier curve fitting. The modeling approach uses Bézier curve fitting three times: Bézier contours in short axis slices, longitude, and latitude Bézier contours. The resulting model will be used as the initial segmentation for the subsequent deformable model-based segmentation.

2.D. Deformable model-based segmentation

The myocardial model described above not only provides a good initial segmentation result, thus avoiding local minima, but also provides a shape constraint for the subsequent deformable model-based segmentation. The myocardium in the low dose CT image does not demonstrate strong edges, but shows strong Gaussian distribution of the intensity. We develop an energy function to govern the evolution of the initial model by exploring both the region information and the shape

constraints,

$$E(u) = \lambda_1 \frac{1.0}{|\Omega_u|} \iiint_{\Omega_u} (I(x, y, z) - \bar{I})^2 d\Omega + \iint_{\partial\Omega_u} Lu(x, y, z) dS - \lambda_2 |\Omega_u|, \quad (6)$$

where u is the unknown deformation field. Ω_u is the region surrounded by surface $\partial\Omega_u$, which is the initial surface (Bézier model) deformed by u . L is a smoothing operator. $\bar{I}$ is the mean intensity of image I within Ω_u . The first term measures the variation of the intensity in the region and the second term measures the smoothness of the deformation field applied to the initial model or the change of the initial shape. In another word, any rigid movements or isotropic scaling of the model do not impose penalty. The third term measures the volume of the region to avoid being too close of the epi and endo surfaces caused by the isotropic shrinking of the two surfaces. When E reaches the minimal, a region characterized by (1) grouping voxels with similar intensity, (2) smoothly deviated from the initial model, and (3) including as many voxels as possible, will be found. The variation of the intensity and the size of the cluster are controlled by λ_1 and λ_2 , respectively. To effectively find the numeric solution, function (6) is approximated by representing the unknown region Ω_u with the region, denoted by R_{M_D} , surrounded by a mesh M_D . The evolution of the mesh is restricted in the normal direction, i.e., for a vertex v_i , it only moves along its normal direction as shown in Fig. 6(b) with a distance d_i . This approximation is able to maintain the mesh quality as evolving and significantly lower the computational cost of optimizer since moving on the mesh surface does not contribute to minimizing the energy function. D is the vector concatenated from d_i . M_D denotes the mesh evolving from the initial mesh, produced by Bézier modeling, with a distance vector D . Smoothing operator L is approximated by the degree of the relative movement between the current vertex and its neighboring vertices. As a result, function (6) is approximated by

$$E(D) = \lambda_1 \frac{1.0}{|R_{M_D}|} \sum_{i,j,k \in R_{M_D}} (I(i, j, k) - \bar{I})^2 + \sum_{v \in S_{M_D}} \left(d_v - \frac{1}{|N_v|} \sum_{s \in N_v} d_s \right)^2 - \lambda_2 |R_{M_D}|, \quad (7)$$

where S_{M_D} is the surface of mesh M_D , N_v is the neighboring set of vertex v , and $|R_{M_D}|$ is the number of voxels within mesh M_D . The set of the voxels within M_D can be calculated by voxelization, a rasterization technique. Function (7) is solved by the gradient-based L-BFGS optimizer, suitable for high-dimensional optimization problems.²²

2.D.1. Performance issues

The main computations involved in energy function (7) are the intensity variance and the voxelization. Both computations are time consuming, leading to the gradient computation of the L-BFGS optimizer intensive. Voxelization is

FIG. 6. Tetrahedral mesh and search direction. (a) construct six connected tetrahedron mesh based on the center o_i and its new position o'_i . (b) search direction of the outer surface (left) and inner surface (right).

computationally intensive because it needs to loop over all voxels within a bounding box of the surface mesh to determine if one voxel is within the surface mesh or not. To calculate the variance, all voxels within the mesh need to be visited at least once (the mean value can be obtained as we perform voxelization). For a typical CT image with size $512 \times 512 \times 47$, the running time of the optimizer can reach a couple of hours without an efficient algorithm to calculate the gradient. Assume the size of the parameter space, i.e., the number of the vertices is S , the number of iteration of L-BFGS is N , the i th component of D is d_i , and the current parameter is $\hat{D}$, the partial derivative with respect to d_i can be approximated by center difference

$$\frac{\partial E}{\partial d_i} = \frac{E(\hat{D} + \Delta D_i) - E(\hat{D} - \Delta D_i)}{2d_i},$$

where ΔD_i is a vector with the i th component nonzero and all the other components zero.

The computational time spending on the gradient $\frac{\partial E}{\partial \hat{D}}$ is approximately $2 \times S \times N \times (T_{\text{variance}} + T_{\text{voxelization}})$. For a CT image with size $512 \times 512 \times 47$, the myocardial model with longitude resolution of 36 and latitude resolution of 36 will have $36 \times 36 + 1 = 1297$ (one apex) parameters. The time used for the calculation of the variance and voxelization on a workstation equipped with 2-core Intel Xeon CPU, 2.83 GHz, 8.00 GB RAM is about 0.1 s and 0.3 s, respectively. Thus, the total time of the $\frac{\partial E}{\partial \hat{D}}$ for 20 iterations is about $2 \times 1297 \times 20 \times \frac{(0.1+0.3)}{3600} = 5.76$ h, which is unacceptable for clinical practice. Because the change of the energy function value is related to the change of the geometry of the mesh, to reduce the computational time, for each vertex o_i , we first build its clique as shown in Fig. 6(a). All the cells within the clique share the same vertex o_i . Assume o_i moves to o'_i by a distance d_i along its normal direction, the cells within the clique along with o'_i will constitute six tetrahedra. We use M_{d_i} to denote these six tetrahedra resulting from the distance d_i . The voxels within M_{d_i} can be obtained by looping over all tetrahedra and find voxels within each tetrahedron. Let $N_{M_{d_i}}$ denote the number of voxels in M_{d_i} , $N_{M_{\hat{D}}}$ denote the number of voxels in mesh $M_{\hat{D}}$ with current parameter $\hat{D}$, and $\bar{I}_{M_{\hat{D}}}$ denote the mean intensity value within $M_{\hat{D}}$, the mean value

within $M_{\hat{D}} + M_{d_i}$, i.e., $\bar{I}_{M_{\hat{D}}+M_{d_i}}$ can be calculated as

$$\bar{I}_{M_{\hat{D}}+M_{d_i}} = \frac{N_{M_{\hat{D}}}}{N_{M_{\hat{D}}} + N_{M_{d_i}}} \bar{I}_{M_{\hat{D}}} + \frac{N_{M_{d_i}}}{N_{M_{\hat{D}}} + N_{M_{d_i}}} \bar{I}_{M_{d_i}}.$$

The variance [the first term of function (7)] within $M_{\hat{D}} + M_{d_i}$ can be calculated as

$$\begin{aligned} & \frac{1}{N_{M_{\hat{D}}} + N_{M_{d_i}}} \sum_{i,j,k \in M_{\hat{D}}+M_{d_i}} (I(i,j,k) - \bar{I}_{M_{\hat{D}}+M_{d_i}})^2 \\ &= \frac{1}{N_{M_{\hat{D}}} + N_{M_{d_i}}} \sum_{i,j,k \in M_{\hat{D}}} (I(i,j,k) - \bar{I}_{M_{\hat{D}}+M_{d_i}})^2 \\ & \quad + \frac{1}{N_{M_{\hat{D}}} + N_{M_{d_i}}} \sum_{i,j,k \in M_{d_i}} (I(i,j,k) - \bar{I}_{M_{\hat{D}}+M_{d_i}})^2. \end{aligned}$$

The second term is the variance within M_{d_i} . Define $\Delta I = \bar{I}_{M_{\hat{D}}+M_{d_i}} - \bar{I}_{M_{\hat{D}}}$, and the first term can be rewritten as

$$\begin{aligned} & \sum (I - \bar{I}_{M_{\hat{D}}} - \Delta I)^2 \\ &= \sum (I - \bar{I}_{M_{\hat{D}}})^2 - 2\Delta I \sum (I - \bar{I}_{M_{\hat{D}}}) + \Delta I^2 N_{M_{\hat{D}}}. \end{aligned}$$

We notice that both $\sum (I - \bar{I}_{M_{\hat{D}}})^2$ and $\sum (I - \bar{I}_{M_{\hat{D}}})$ can be recorded as we calculating variance at $\hat{D}$. So, there is no need to loop over the image when we calculate the variance at $\hat{D} + \Delta D_i$. It is similar to calculate $E(\hat{D} - \Delta D_i)$. Using the above method, we only need to calculate the number of voxels within M_{d_i} , and the variance within M_{d_i} , which dramatically reduces the computational time from 5.76 h to less than 1 min.

2.E. Nonrigid registration of pre- and postcontrast low dose CT images

To register the precontrast CT with the postcontrast CT, we employed a nonrigid registration method implemented in ITK.²³ To make this paper self-contained, we briefly describe this registration method in this section. This registration method uses free-form deformation (FFD) (Ref. 24) to simulate the underlying deformation and uses normalized cross-correlation (NCC) as the similarity metric. Our purpose is to register the precontrast CT (floating image) with postcontrast CT (reference image). The transform T can be resolved

FIG. 7. ECVF calculation pipeline.

by minimizing the normalized cross-correlation,

$$E(T|C) = \frac{\sum_N (R(p_i) - \bar{R})(F(T(p_i|C)) - \bar{F})}{\sqrt{\sum_N (R(p_i) - \bar{R})^2 \sum_N (F(T(p_i|C)) - \bar{F})^2}}. \quad (8)$$

The T is modeled as a free-form deformation with unknown parameter C . FFD is a piecewise cubic polynomial and can be manipulated by a regular control grid with spacing $s_x \times s_y \times s_z$ for a 3D image. FFD is computationally efficient, because the deformation at any point is only influenced by its surrounding $4 \times 4 \times 4$ control points. For a point p with coordinate (x, y, z) , assume its $4 \times 4 \times 4$ control points are p_{ijk} , $i, j, k = 0 \dots 3$, and denote d_{ijk} as the unknown displacement vector associated with the control point p_{ijk} , the displacement of point p is defined as

$$T(p|d_{ijk}) = \sum_{i=0}^3 \sum_{j=0}^3 B_i(u)B_j(v)B_k(w)d_{ijk}, \quad (9)$$

where

$$u = \frac{x}{s_x} - \left\lfloor \frac{x}{s_x} \right\rfloor, v = \frac{y}{s_y} - \left\lfloor \frac{y}{s_y} \right\rfloor, w = \frac{z}{s_z} - \left\lfloor \frac{z}{s_z} \right\rfloor.$$

Here B_i is the i th basis function of BSplines. We use a vector C to denote the concatenation of d_{ijk} , which can be resolved by minimizing function (8) using L-BFGS optimizer.²²

2.F. ECVF calculation

Figure 7 illustrates the pipeline to calculate ECVF based on Eq. (5) using the aligned precontrast CT, postcontrast CT, and the myocardial model. The 17-segments are produced based on the standard left ventricular segmentation suggested by AHA (Ref. 21) [see Fig. 8(a)]. Producing the 17-segments from the proposed model is straightforward since each node

of the model can be represented by its longitude and latitude indexes.

Assume the longitude resolution of the model is r_{long} , the height from the bottom to the apex of the endocardium is h_{endo} , the height from the bottom to the apex of the epicardium is h_{epi} , the distribution of the latitudinal indexes of the four segments are: basal: $[0, \frac{h_{\text{endo}}}{3} \times r_{\text{long}}]$, mid: $[\frac{h_{\text{endo}}}{3} \times r_{\text{long}}, \frac{2h_{\text{endo}}}{3} \times r_{\text{long}}]$, apical: $[\frac{2h_{\text{endo}}}{3} \times r_{\text{long}}, h_{\text{endo}}]$, and apex: $[h_{\text{endo}}, h_{\text{epi}}]$. In the longitudinal direction, we separate the basal and mid segments into six segments and apical segments into four segments as shown in Fig. 8(a). Assume the latitude resolution of the model is r_{lati} , the distribution of the longitudinal indexes of the basal segments are: segment 1: $[0, \frac{r_{\text{lati}}}{6}]$, segment 2: $[\frac{r_{\text{lati}}}{6}, \frac{r_{\text{lati}}}{3}]$, segment 3: $[\frac{r_{\text{lati}}}{3}, \frac{r_{\text{lati}}}{2}]$, segment 4: $[\frac{r_{\text{lati}}}{2}, \frac{2r_{\text{lati}}}{3}]$, segment 5: $[\frac{2r_{\text{lati}}}{3}, \frac{5r_{\text{lati}}}{6}]$, and segment 6: $[\frac{5r_{\text{lati}}}{6}, 0]$. Similarly, we can get the longitudinal index distribution for the other three segments. The order and orientation of 17-segments is determined by that of the basal segment as shown in Fig. 8(b), in which two right ventricle insertion points can uniquely define the order and orientation. The first and third points selected by clinician correspond to these two insertion points. We allow one point between these two insertion points in order to get a smooth Bézier curve as shown in Fig. 8(c).

After producing the 17-segments model, voxelization is used to locate voxels in each segment of the model, and each voxel is assigned with corresponding label to generate a 17-segments map (see Fig. 7). Three blood pools (spheres) are detected within the endocardium model. The centers of the three blood pools correspond to the geometry centers of the three segments along the vertical long axis: basal, mid-cavity, and apical segments as shown in Fig. 5 and the radius are specified by clinicians. These three blood pools offer the flexibility to calculate $\Delta\text{HU}_{\text{Blood}}$ for each segment. After blood pools are identified, ECVF map can be calculated using

FIG. 8. Seventeen-segments of left ventricular suggested by Ref. 21. (a) Circumferential polar plot of 17-segments. (b) 6 basal segments. (c) point selections to produce 17-segments. Id1 and Id3 correspond to two right ventricle insertion points. Figures (a) and (b) reproduced by permission from American Heart Association, *Circulation* **105**(4), 539–542 (2002). Copyright 2002.

Eq. (5). The ECVF map can be used with 17-segments map for the statistics analysis of the ECVF for each segment, or used with the 17-segments model for visualization.

2.G. An integrated ECVF toolkit: ECVTK

An integrated ECVF analysis environment as shown in Fig. 9(a) was developed to incorporate the myocardial modeling, deformation model segmentation, nonrigid registration, ECVF calculation, visualization, and statistics report into one software system. ECVTK supports multiple image formats (DICOM3, Analyze, Meta, JPET, PNG) and geometrical data formats (vtk, vtp, stl) and organizes all data in a tree structure. Visualization module has a 3D rendering window and three 2D rendering windows. Both image data such as ECVF map and geometry data such as the myocardial model can be visualized simultaneously in these four windows. The ECVF report is organized into an XML file, which contains Mean $\pm$ Std of ECVF and myocardium attenuation of all

17-segments. A mesh editor tool is also provided to allow users to freely adjust the myocardial model [illustrated as Fig. 9(b)] in case of failure of the deformable model-based segmentation.

2.H. Imaging protocol and statistical analysis

2.H.1. Cardiac MR imaging protocol

All MRI Images were obtained with a 3-Tesla scanner (Verio; Siemens, Erlangen, Germany) with a 32-channel array coil (InVivo, Gainesville, FL). A modified Look Locker with inversion recovery sequence (MOLLI) was used for cardiac T1 measurement. Scanning parameters were as follows: TR/TE1.9/1.0 ms; inversion time increment, 80.0 ms; field of view, 290–360 mm²; readout resolution, 192; phase resolution, 75%–85%; slice thickness, 8 mm; flip angle, 35°; and parallel imaging acceleration factor, 2. MOLLI images were obtained at the base, middle, and apical levels of the left ventricle in short axis view. Images for T1

FIG. 9. ECVTK and Mesh editor. (a) ECVTK GUI including Data tree, Model/Volume visualization control, Image processing and 2D/3D visualization panels. (b) Mesh editor. The top images show the drag of the red point of the 2D myocardial boundary leads to the local geometrical change of the 3D model. The bottom images show the Gaussian kernel interpolation of the vertex displacement based on the dragged point.

FIG. 10. Intermediate and final results of the segmentation. (a) Wireframe view of the initial mesh with parameters: longitudinal resolution 36 and latitudinal resolution 36. (b) Surface view of the initial model. (c) Initial model (white model) evolves to the final model (black model). (d) Initial contour (white contour) evolves to the final contour (black contour) in the short axis slice.

measurements were obtained before and after intravenous bolus infusion of gadopentetate dimeglumine (0.15 mmol/kg, Magnevist; Bayer Healthcare Pharmaceuticals, Wayne, NJ). Postcontrast MOLLI acquisition was performed at the same positions as precontrast examinations 12 and 25 min after injection. To assess left ventricular function, steady-state free precession cine MR images were acquired. Phase-sensitive inversion-recovery late gadolinium enhanced MR imaging was performed to assess for focal myocardial scar.³

2.H.2. Cardiac CT protocol

All CT images were acquired on a 320-MDCT scanner (Aquilion One, Toshiba Medical Systems, Tustin, CA) following the CMR examination. A precontrast calcium score type acquisition was performed with the use of prospective ECG gating with a 350 ms single gantry rotation during inspiration breath hold that allows image acquisition at a single cardiac phase. Scanning parameters were: tube voltage 120 kV, tube current 300 mA, 0.5 mm slice thickness. After a 7–10 min delay, a postcontrast CCT scan was acquired with identical parameters as the precontrast “calcium score” scan.

2.H.3. Statistical analysis

To examine the bias and limits of agreement between ECVF at cardiac MR and ECVF at cardiac CT, the Bland-Altman method was employed. Interobserver vari-

ability of the segmentation was accessed using concordance correlation coefficient (CCC) with two-way random model ($CCC < 0.40$ = poor; $0.40 \leq CCC \leq 0.75$ = fair to good; $CCC > 0.75$ = excellent agreement).

3. RESULTS

In this section, we first conducted experiment to evaluate the accuracy of the segmentation method; and then evaluated its interobserver variability; finally, we compared the ECVF of the proposed framework with that of the cardiac MR used Pearson correlation and linear regression.

3.A. Evaluate the accuracy of myocardium segmentation

A total of 20 cases were included for the evaluation of the myocardium segmentation. The reference (ground truth) was produced by manual segmentation using our mesh editing tool. Each case was segmented by two observers using the same segmentation method to show the interobserver variability of the proposed method.

Figure 10 shows the mesh evolution in 3D (left figure) and 2D (right figure) spaces, from the initial white mesh, produced by our point-based modeling method, to the final black mesh, produced by our deformable model-based segmentation.

Figure 11 shows the segmented myocardium in the short axis slice (left two figures) and the long axis slice (right two

FIG. 11. Deformable model segmentation results. White contour is the result produced by the proposed method, and the black contour is the reference contour. (a) A 61 years old female, short axis slice. (b) A 44 years old male, short axis view (c) A 45 years old female, long axis slice. (d) A 54 years old female, long axis view.

FIG. 12. Quantitative evaluation of the accuracy of the segmentation method regarding TPVF (a), FPVF (b), and ASD (c), and the running time (d) for 20 cases. The interobserver variability is measured by CCC. TPVF, FPVF, ASD, and CCC.

figures) for four different cases. The black contour is the reference result, produced by an expert by manually adjusting myocardial surface. The white contour comes from the automatic segmentation method.

The quantitative evaluation of the accuracy was performed regarding true positive and false positive volume fractions (TPVF and FPVF),²⁵ and average surface distance (ASD). TPVF indicates the fraction of the total amount of tissue inside the reference delineation, and FPVF denotes the amount of tissue falsely identified. They are defined as follows:

$$\text{TPVF} = \frac{|S_{\text{seg}} \cap S_{\text{ref}}|}{|S_{\text{ref}}|}, \text{FPVF} = \frac{|S_{\text{seg}} - S_{\text{seg}} \cap S_{\text{ref}}|}{|S_{\text{whole}} - S_{\text{ref}}|}, \quad (10)$$

where S_{seg} denotes the extracted voxel set in the segmented image, S_{ref} denotes the extracted voxel set in the reference image, and S_{whole} denotes the voxel set in the whole image. $|\cdot|$ is the cardinality measure of a set. As shown in Fig. 12, for the first observer, the TPVF is $92.39\% \pm 3.44\%$, FPVF is $0.3\% \pm 0.1\%$, and ASD is 0.68 ± 0.13 mm, and for the second observer, the TPVF is $91.96\% \pm 3.67\%$, FPVF is $0.31\% \pm 0.11\%$, and ASD is 0.69 ± 0.15 mm. The CCC of TPVF, FPVF, and ASD are 0.95, 0.90, 0.94, respectively, demonstrating excellent agreement.

3.B. ECVF evaluation

Twenty subjects were involved in our study. The mean age in this population was 63.2 years (range, 45–95 years). The slice thickness is 3 mm and inplane pixel size is 0.37×0.37 mm. The image size is $512 \times 512 \times 47$.

Figure 13 shows the ECVF results of a 48 years old male patient with heart failure. Figure 13(a) clearly shows a region with elevated ECVF on the apical section, and Fig. 13(b) shows the same region of elevated ECVF from the view of endo surface. For each segment, we calculate its average ECVF and show the average 17-segments in Fig. 13(c) with polar plot and Fig. 13(d) with the model, in which segments 13–17 show elevated average ECVF. The global ECVF and the ECVF of each segment are listed in the first row of Table I. Comparing with the ECVF of the normal volunteer (the second row of Table I), the patient with heart failure shows much higher ECVF in segments of 13–17.

Figure 14 shows the ECVF results of a 53 years old female normal volunteer. Both Figs. 14(a) and 14(b) demonstrate homogeneous normal ECVF regions in both epi and endo surfaces. Both Figs. 14(c) and 14(d) show the average normal ECVF.

The Bland-Altman method was used to calculate bias and limits of agreement. The 95% limits of agreement between the two methods range from -10.5% and 12.6% . A small bias (1.1%) toward higher ECVF was detected for cardiac CT (Fig. 15).

FIG. 13. ECVF results of a 48 years old male patient with heart failure. (a) The ECVF at the epicardium viewed from the outside. (b) The ECVF at the endocardium viewed from the base. Three blood pools are also visualized. (c) The ECVF 17-segments polar plot. (d) Average ECVF of each segment on the surface (total 17 segments). The arrows correspond to the elevated ECVF regions on epi surface (a), endo surface (b), polar plot (c), and 17-segments model. The ECVF is mapped to the color. The black color denotes a small ECVF and the white color denotes a larger ECVF.

TABLE I. ECVF statistical report for one normal subject and one abnormal subject. Each subject has a global ECVF (GECVF) and 17 average segment ECVFs. Both subjects have the same $Hct_{\text{blood}} = 0.43$. Segments 13–17 show elevated average ECVF highlighted by boldface.

	GECVF	Seg1	Seg2	Seg3	Seg4	Seg5	Seg6	Seg7	Seg8	Seg9	Seg10	Seg11	Seg12	Seg13	Seg14	Seg15	Seg16	Seg17
Abnormal	41.98	32.27	38.00	34.13	30.99	38.97	30.55	31.58	37.91	32.87	32.00	41.71	28.38	68.56	65.53	57.46	47.96	68.52
Normal	34.29	29.06	34.77	34.54	36.49	33.18	29.82	28.70	34.47	37.81	43.87	34.59	27.79	29.78	33.58	38.51	32.72	35.35

FIG. 14. ECVF results of a 53 years old female normal volunteer. (a) The ECVF model viewed from the outside. (b) The ECVF model viewed from the base. (c) The ECVF 17-segments polar plot. (d) Average ECVF of each segment on the surface.

FIG. 15. Agreement between ECVF at CMR and CCT. Bland-Altman plot shows 95% limits of agreement between the two methods of -10.5% and 12.6% (dashed line). There is a small bias (1.1%) toward higher ECVF at CCT (black line).

4. CONCLUSION

Diffuse myocardial fibrosis is a common endpoint of most cardiomyopathies, and early collagen deposition is known to be reversible in animal studies. ECVF quantification is a promising biomarker for risk predication, as well as incremental support to patient management. It may also guide us toward effective therapy to reduce or reverse the development of diffuse myocardial fibrosis at an early stage. To address the challenges induced by the low dose CT images, in this paper, we presented an ECVF calculation framework consisting of a point-guide modeling, a deformable model-based myocardium segmentation, nonrigid registration, and ECVF calculation. The point-guide modeling is able to use sparse points to build a patient specific model with easy implementation since the core operation of the modeling is only Bézier curve fitting. The model-based segmentation explores the region information contained in the image and the shape constraint imposed by the patient specific model, therefore effectively avoiding the influence of the noise and poor image

quality. The segmentation method was evaluated regarding the accuracy and interobserver variability. The entire framework was evaluated on 20 patients and the results demonstrated the accuracy and robustness of the segmentation method. There is good agreement between the ECVF calculated by the proposed framework and the ECVF measured by cardiac MR imaging. Given the increasing importance of cardiac CT, this work is exciting in its potential to provide a much more efficient, accurate, and widely available noninvasive measure of diffuse myocardial fibrosis.

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