**ONLINE SUPPLEMENT**

**1. Data acquisition**

As our study was designed as a proof of concept, the 61 patients were selected such that the number of patients with and without events roughly matched. Fig. 1 in this supplement displays the 2D short-axis slices of the LGE-CMR image acquired for an example patient. The figure illustrates that, due to the limited resolution of the image in slice thickness, the apex of the heart is not visible in the image. Therefore, AHA region 17 was excluded from all statistical analyses in this study.



Figure1. The image slices from base (left) to apex (right) acquired for an example patient. The slice thickness of the image is 8mm.

**2. Reconstruction of 3D LV geometry**

The semiautomatic contouring of the LV endocardium and epicardium was performed using CineTool® (General Electric Healthcare). The landmarks corresponding to the RV insertion points were placed using a graphical user interface developed in-house in MATLAB® (Mathworks, Inc.). The 2D binary masks that implicitly represented LV endocardium and LV epicardium were constructed by labeling the pixels that lied within the contours. To construct the 2D mask for septal endocardium in each slice, two rays that start from the centroid of the endocardium and pass through the landmark points were computed, and the pixels that lied between the rays marked. We used a variational implicit functions strategy to interpolate each set of 2D masks to build a 3D binary mask at 1mm isotropic resolution. In this interpolation strategy, for each set of 2D masks, a 3D thin plate spline function was defined such that was a linear combination of radial basis functions of the form , at pixels along the perimeters of the masks, and at pixels that are adjacent to the perimeter pixels and inside the mask. The coefficients of the linear combination were calculated by solving the linear system that results from enforcing the boundary constraints. More details on this interpolation method are available elsewhere.[1](#_ENREF_1) By discretizing the 3D functions, and thresholding for values above 0, 3D masks for LV endocardium, LV epicardium, and septal endocardium were generated. Finally, the geometry image of the LV wall was generated by combining the 3D masks. The final geometry image had different intensities for the LV chamber, LV free-wall, and septum.

**3. Computation of shape metrics**

The principal curvature values were computed as described in Goldman.[2](#_ENREF_2) Given a surface implicitly represented as an isosurface of a function *g* in 3D, the principal curvatures at each point on the surface are given by

where and denote the gradient and Hessian of , and is the identity matrix. We evaluated two options for , namely the 3D thin plate spline function , and a Gaussian-smoothed version of the 3D mask, where both and the mask were built from the set of 2D binary masks corresponding to the endocardium as described in section 2 of this online supplement. We adopted the latter option because it was found to be less susceptible to noise. Curvedness of the endocardial surface was defined as the root mean square of its principal curvatures, i.e.,

Note that, at all points on a sphere with radius , both and equal , and therefore, curvedness is also as per the above formula.[2](#_ENREF_2) In general, curvedness is the inverse of radius.[3](#_ENREF_3)

RWT was computed as the product of WT and curvedness, i.e.,

.

**4. Segmentation of patient endocardial surface**

In computational anatomy, an atlas is a representative anatomy which can be deformed to match different patient anatomies. Computational anatomy atlases are typically labeled with pertinent data such as various anatomical regions, just as a world atlas is overlaid with geographical features. In our work, the atlas was labelled with AHA regions using a variant of the segmentation methodology described in Su, et al.[4](#_ENREF_4) In this variant, we divided the 3D atlas geometry into apex, apical level, mid level, and basal level with 3 planes, all parallel to the short axis imaging plane. The first of the 3 planes passed through the most apical point of the LV chamber, the second was located 1/3rd the way from the first plane to the most basal short axis image plane, and the third 2/3rd the way from the first plane to the most basal short axis image plane.

The atlas LV wall in each short axis basal slice was then divided into 6 regions. To perform this division, a reference direction that pointed from the centroid of the LV chamber to the midpoint of the endocardial contour that belonged to the septum was computed. Then, for each voxel in the LV wall, the clockwise angle between the reference direction, and the vector that connected the centroid and the voxel was computed. The voxel was labelled as belonging to AHA regions 1-6 based on this angle. Similarly, the LV wall in mid and apical levels were labelled with AHA regions 7-12, and 13-16, respectively.

The deformation of the atlas to match a patient geometry was achieved using a combination of affine transformation and multi-channel large deformation diffeomorphic metric mapping (MC-LDDMM).[5](#_ENREF_5) In the affine transformation, each 3D point in the atlas is moved to a point according to the equation

,

where is a 3x3 matrix, and a 3x1 vector. The elements of and were computed based on a set of corresponding landmark points identified in the atlas and patient geometries. Seven anatomical landmarks, including the apex, the centroid of the LV chamber at the base, the two RV insertion points at the base, and three points that evenly divided the epicardial contour of the LV free-wall at the base were used. More details on landmark-based affine transformations can be found elsewhere.[6](#_ENREF_6)

The affine transformation provided an initial registration for MC-LDDMM, which deformed the affine-transformed atlas geometry further to match the patient geometry, using a diffeomorphic (invertible and smooth) transformation. In brief, given the affine-transformed atlas image and the patient image , MC-LDDMM computes a flow of diffeomorphisms to transform to match , where is the 3D cube in which the image data are defined, , and is a smooth, compactly supported, time-dependent velocity vector field such that

.

The initial diffeomorphism is the identity transformation. The final diffeomorphism is calculated by integrating the optimal vector field given by

Here, is the number of channels, and denotes image corresponding to the channel in the atlas. In the present work, we employed the 3D endocardial, epicardial, and septal masks as channels. The norm is defined as to enforce smoothness on the vector fields , where is a differential operator of the Cauchy-Navier type. The parameters and control the elasticity of the transformation, and is the norm of square integrable functions defined on . The optimal solution is computed by means of a gradient descent search. The diffeomorphic property of MC-LDDMM guarantees that the atlas does not “fold over” itself during deformation, thereby preserving the integrity of anatomical structures. For detailed mathematical descriptions of the MC-LDDMM algorithm and implementation, the reader is referred to previous publications.[5](#_ENREF_5), [7](#_ENREF_7)

To segment the endocardial surface of each patient based on infarct transmurality, the infarct zone in each 2D slice of the patient LGE-CMR image needed to be planimetered, and the result used to reconstruct a 3D geometry of the infarct. For the planimetry, a trained observer identified a region of interest (ROI) in the remote, non-infarcted myocardium, and computed the maximum image intensity in this ROI as the peak remote intensity. The observer then loosely outlined the hyper enhanced region, and all voxels in this region with intensity above the peak remote intensity was labeled as belonging to the infarct zone. For a more detailed description of the planimetry, please refer to a previous publication.[8](#_ENREF_8)

To reconstruct infarct geometry in 3D, each 2D slice after planimetry was converted into a grayscale image, where each pixel was assigned a value whose magnitude was the distance to the nearest point on the infarct zone boundary. The sign of this assigned value was negative if the pixel was within the infarct zone, and positive if outside. The 2D slices were then interpolated linearly to obtain a 3D image, which was then thresholded for values below zero, to obtain a 3D binary image of the infarct geometry. More details on this reconstruction technique can be found elsewhere.[9](#_ENREF_9)

**5. Statistical analyses**

Even though we could have assessed the inter-group shape differences in each independent AHA region, the statistical comparisons were performed in the 3 coronary artery regions. Analysis by coronary artery regions is physiologically very meaningful in the context of myocardial infarction, as the segments are inter-related and dependent. This approach also significantly (by a factor of over 5) reduces the number of simultaneous statistical comparisons, and thereby decreases the probability of multiple comparison (Type I) errors. The mean of each shape metric in each region (coronary artery regions, as well as transmurally infarcted regions and the rest) of the endocardial surface of each patient was computed as

where is the number of voxels in the region, and is the value of the shape metric at voxel in the region. All statistical analyses were performed using non-parametric methods, including the Kruskal-Wallis and Wilcoxon tests,[10](#_ENREF_10) in the MATLAB® (Mathworks, Inc.) computing environment. Unpaired tests were used for between-group comparisons, and paired tests for within-group comparisons. A significance level of was used.

The mean shape metrics were corrected for confounding effects of covariates, by fitting a linear regression model that predicts the former by the latter, and taking the residual. It is important to perform such a correction, as demonstrated elsewhere in the context of shape analysis of brain structures.[11](#_ENREF_11), [12](#_ENREF_12) In the present study, we used presence of diabetes, and duration of cardiomyopathy diagnosis as covariates, as these two factors strongly influence ventricular remodeling,[13](#_ENREF_13), [14](#_ENREF_14) and were the least balanced non-structural baseline characteristics between groups. Mathematically, for each coronary artery region of subject , corrected mean curvedness, WT, and RWT were computed as

,

where were the uncorrected mean curvedness, WT, or RWT, and the value of covariate . The coefficients were determined by linear regression. For more details on the correction for covariates, please refer to previous publications.[11](#_ENREF_11), [12](#_ENREF_12)

Correction for multiple comparison errors was incorporated using permutation tests, as described previously.[11](#_ENREF_11), [12](#_ENREF_12), [15](#_ENREF_15), [16](#_ENREF_16) Briefly, for the between-group comparisons in our study, we computed the Wilcoxon rank sum test statistic in each coronary artery region for a large number of random assignments of the group labels to the subjects (i.e., permutations). The maximum test statistic in each permutation was then calculated, and compared with the test statistic obtained with true group labels for each coronary artery region . The *p*-value for coronary artery region was then calculated as the fraction of times exceeded . To correct for multiple comparison errors in our within-group analyses, we employed a permutation test for pairwise comparisons, as published elsewhere.[16](#_ENREF_16) Specifically, a large number of permutations of the sample were generated by swapping the mean shape metric values of the non-transmurally infarcted or normal coronary artery regions with those of transmurally infarcted ones in a randomly selected subset of the group. As before, the maximum test statistic in each permutation was then computed, and compared with the test statistic corresponding to the true shape metrics, to generate a *p-*value for each coronary artery region. As demonstrated by previous research, permutation tests such as the ones we employed make minimal assumptions about the data,[15](#_ENREF_15) are effective in eliminating multiple comparison errors in shape analysis,[11](#_ENREF_11), [12](#_ENREF_12) and are widely used in the statistics community.[16](#_ENREF_16)

**References**

[1] Turk G, O'Brien J: Shape Transformation Using Variational Implicit Functions. Proc. SIGGRAPH 1999; 335 - 342.

[2] Goldman R: Curvature formulas for implicit curves and surfaces. Computer Aided Geometric Design 2005; 22: 632 - 658.

[3] Zhong L, Su Y, Yeo S-Y, Tan R-S, Ghista DN, Kassab G: Left ventricular regional wall curvedness and wall stress in patients with ischemic dilated cardiomyopathy. American Journal of Physiology - Heart and Circulatory Physiology 2009; 296: H573-H584.

[4] Su Y, Zhong L, Lima C-W, Ghistac D, Chua T, Tan R-S: A geometrical approach for evaluating left ventricular remodeling in myocardial infarct patients. Computer Methods and Programs in Biomedicine 2012; 108: 500 - 510.

[5] Ceritoglu C, Oishi K, Li X, Chou MC, Younes L, Albert M, Lyketsos C, Zijl PCv, Miller MI, Mori S: Multi-contrast large deformation diffeomorphic metric mapping for diffusion tensor imaging. Neuroimage 2009; 47: 618 - 627.

[6] Späth H: Fitting affine and orthogonal transformations between two sets of points. Mathematical Communications 2004; 9: 27 - 34.

[7] Beg MF, Helm PA, McVeigh E, Miller MI, Winslow RL: Computational Cardiac Anatomy Using MRI. Magnetic Resonance in Medicine 2004; 52: 1167 - 1174.

[8] Wu KC, Gerstenblith G, Guallar E, Marine JE, Dalal D, Cheng A, Marbán E, Lima JAC, Tomaselli GF, Weiss RG: Combined Cardiac MRI and C-Reactive Protein Levels Identify a Cohort at Low Risk for Defibrillator Firings and Death. Circulation: Cardiovascular Imaging 2012; 5: 178 - 186.

[9] Raya SP, Udupa JK: Shape-based interpolation of multidimensional objects. IEEE Transactions on Medical Imaging 1990; 9: 32 - 42.

[10] Cordor GW, Foreman DI, *Nonparametric Statistics for Non-Statisticians*. New Jersey: Wiley, 2009.

[11] Miller M, Younes L, Ratnanather J, Brown T, Trinh H, Postell E, Lee D, Wang M, Mori S, O'Brien R, Albert M, Team. BR: The diffeomorphometry of temporal lobe structures in preclinical Alzheimer's disease. Neuroimage: Clinical 2013; 3: 352 - 360.

[12] Younes L, Ratnanather J, Brown T, et al.: Regionally selective atrophy of subcortical structures in prodromal HD as revealed by statistical shape analysis. Human Brain Mapping 2012; 35: 792 - 809.

[13] Ishii H, Amano T, Matsubara T, Murohara T: Pharmacological Intervention for Prevention of Left Ventricular Remodeling and Improving Prognosis in Myocardial Infarction. Circulation 2008; 118: 2710-2718.

[14] Bibra v, M SJS: Impact of diabetes on postinfarction heart failure and left ventricular remodeling. Current Heart Failure Reports 2011; 8: 242 - 251.

[15] Good P, *Permutation Tests: A Practical Guide to Resampling Methods for Testing Hypotheses*: Springer, 2000.

[16] Blair R, Karniski W, "Distribution-free statistical analysis of surface and volumetric maps," in *Functional Neuroimaging: Technical Foundations*, R. Thatcher, M. Hallett, T. Zeffiro, E. R. John, and M. Huerta, Eds., ed San Diego: Academic Press, 1994.