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Novel indices for left-ventricular dyssynchrony characterization based on highly automated segmentation from real-time 3D echocardiography

Honghai Zhang^a, Ademola K. Abiose^b, Dipti Gupta^b, Dwayne N. Campbell^b, James B. Martins^b, Milan Sonka^a, and Andreas Wahle^a

Honghai Zhang: honghai-zhang@uiowa.edu; Ademola K. Abiose: ademola@pol.net; Dipti Gupta: dipti-gupta@uiowa.edu; Dwayne N. Campbell: dwayne-campbell@uiowa.edu; James B. Martins: james-martins@uiowa.edu; Milan Sonka: milan-sonka@uiowa.edu; Andreas Wahle: andreas-wahle@uiowa.edu

^aDepartment of Electrical and Computer Engineering, The University of Iowa, Iowa City, IA 52242, USA

^bDepartment of Internal Medicine, The University of Iowa, Iowa City, IA 52242, USA

Abstract

Cardiac resynchronization therapy (CRT) using a biventricular pacemaker is an invasive and expensive treatment option for left ventricular mechanical dyssynchrony (LVMD). The CRT candidate selection is a crucial issue due to the unreliability of the current standard CRT indicators. Real-time 3D echocardiography (RT3DE) provides 4D (3D+time) information about the LV and is suitable for LVMD assessment. In this paper, the complex LV shape and motion of 50 RT3DE datasets are represented by novel 4D descriptors—4D sphericity, volume, and shape, from which novel indices were derived by principal component analysis (PCA) and subsequently analyzed by a support vector machine (SVM) classifier to assess their capability of LVMD characterization and CRT outcome prediction. These novel indices outperformed clinical indices and have promising capabilities in disease characterization and great potential in CRT outcome prediction. To enable efficient quantitative RT3DE analysis, a segmentation method was developed to combine the powers of active shape models and optimal graph search. Various aspects of the method were designed to handle varying RT3DE image quality among datasets and LV segments. An application with graphical user interface was developed to provide the user with simple and intuitive control. The developed method was robust to inter-observer variability and produced very good accuracy— 3.2 ± 1.1 mm absolute surface positioning error, <1 mm mean signed error, and $<5\%$ mean volume difference. The computer method's classification performance was compared with the independent standard, showing that the 4D shape modal indices were not only the most capable of all tested options when employed for disease characterization but also the least sensitive to segmentation imperfections.

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Correspondence to: Honghai Zhang, honghai-zhang@uiowa.edu.

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Keywords

real-time 3D echocardiography; left ventricular mechanical dyssynchrony; cardiac resynchronization therapy outcome prediction; disease characterization; active shape model; optimal graph search segmentation

Introduction

Congestive heart failure with reduced ejection fraction (EF) is often accompanied by loss of coordinated contraction of the left ventricle (LV)—referred to as left ventricular mechanical dyssynchrony (LVMD)—which prompted the development of cardiac resynchronization therapy (CRT) using a biventricular pacemaker as a therapeutic option. Selecting the most suitable candidates for CRT is a crucial issue due to its invasive nature and high cost. Real-time 3D echocardiography (RT3DE) is an appealing new tool for LVMD assessment, providing 4D volumetric (3D+time) LV datasets composed over four cardiac cycles.

This paper focuses on two key technologies of LVMD assessment using RT3DE: 1) developing novel 4D indices to quantify LVMD characteristics and improve CRT prediction, 2) developing a highly-automated segmentation method for RT3DE data.

LVMD characterization and CRT outcome prediction

The current standard CRT indications are: New York Heart Association (NYHA) class III or IV heart failure, left ventricular ejection fraction (LVEF) $\geq 35\%$, QRS duration ≥ 120 ms, and stable medical regimen. Various studies have shown these criteria to be inadequate because 30% of CRT implanted patients are non-responders (Abraham et al., 2002; Bax et al., 2004) while another 30% of LVMD patients currently considered unsuitable for CRT may actually benefit from this treatment (Achilli et al., 2003).

Many dyssynchrony indices derived from traditional 2D or 2D+time echocardiography techniques have been proposed, but a recent multicenter study (Chung et al., 2008) indicated that none of them, if used individually, showed clear improvement in CRT candidate selection beyond the standard criteria.

Recently LVMD assessment using RT3DE data began to show its advantage over 2D or 2D+time echocardiography. The *systolic dyssynchrony index (SDI)*—the standard deviation of the time (percentage of the cardiac cycle) taken to reach minimum volume for each of the 16 segments corresponding to the recommendations of the American Heart Association (AHA) (Cerqueira et al., 2002)—has been proposed as a new method of quantifying global LVMD (Kapetanakis et al., 2005; Soliman et al., 2009) using RT3DE data, but its clinical value is still not very clear (Delgado and Bax, 2011; Sung and Foster, 2011). It has been shown that patients without QRS widening but with LVMD identified by RT3DE indeed benefited from CRT. Furthermore, the mechanical dyssynchrony measured by RT3DE has been shown to have a good correlation with invasively determined acute haemodynamic response to biventricular pacing in patients with symptomatic dilated cardiomyopathy (van Dijk et al., 2008).

The motion of the LV over the cardiac cycle is complex and involves several individual components (Huang et al., 1999). Consequently, the contraction patterns are often quite complicated, especially in ischaemic cardiomyopathy. Even segments of the same wall may exhibit dyssynchrony relative to each other. The reported traditional echocardiography and RT3DE analysis methods each have several fundamental limitations: 1) the derived indices only partially describe the complicated ventricular shape and motion, a lot of information

present in the acquired dataset is not used and ends up discarded; 2) the characteristics of LVMD, how it affects various aspects of the cardiac shape and motion, is not thoroughly studied; 3) the CRT outcome prediction is limited to applying hard threshold on a single or a very small number of indices, the potential of using more sophisticated classifiers as well as the combination of all available quantitative indices are not fully explored.

In this paper, the shape and motion patterns of LV and its segments are characterized by several novel quantitative indices derived from principal component analysis (PCA) of 4D sphericity, volumes and shapes. We assessed the capability of these indices in: 1) capturing LVMD induced shape and motion features, 2) identifying and tracking the reverse remodeling process of LV after CRT, and 3) improving CRT outcome prediction. We have previously reported a small subset of preliminary results on PCA (Zhang et al., 2010b) and sphericity indices (Gupta et al., 2011).

RT3DE Segmentation

Manual tracing of RT3DE is a very tedious process, the accuracy of which can directly impact the CRT prediction. A reliable RT3DE segmentation technique is therefore an essential requirement for quantitative LVMD assessment. However, RT3DE segmentation is a very challenging task due to the large variability of RT3DE image quality caused by speckle noise, signal dropouts and shadowing, limited field of view, and artifacts introduced by limited ultrasound penetration and subvolume stitching.

Several commercial tools, such as TomTec 4D LV-Analysis, Philips QLab 3DQ-Advanced, Toshiba Artida 3D wall motion tracking, and GE 4D LVQ, utilize semi-automatic segmentation techniques that are initialized by several manually defined 2D contours or locations for apex, mitral valves etc. The user often has no further control of the segmentation algorithm besides the initialization. In addition, the segmentation results cannot be exported for further quantitative analysis.

Many 3D and 4D segmentation methods have been proposed by various research groups. A recent review by Leung and Bosch (Leung and Bosch, 2010) summarizes the state of the art in this field and reports that comparing the performance of different methods is difficult due to the lack of well-validated data and large variability of the quality of the images that were segmented.

In a previous preliminary study (Zhang et al., 2010a), we demonstrated the feasibility of RT3DE segmentation method that combines active shape model (ASM) (Cootes and Taylor, 1992) and optimal graph search (Li et al., 2005, 2006). In this paper, such method is further improved and fully evaluated. 1) The cost function for graph search is redesigned with terms, the parameters of which are defined and trained to deal with varying image quality among LV segments. 2) An application with graphical user interface was developed to provide the user with simple and intuitive controls the algorithm. 3) The segmentation accuracy is evaluated by traditional metrics (surface positioning error, volume overlap, etc.) and additional metrics that assess the relationship between segmentation errors and image quality. 4) Sensitivity analyses are performed to determine effects of inter-observer variability on segmentation accuracy as well as segmentation errors on LVMD characterization and CRT outcome prediction.

Shape and Motion Analysis

The LV shape and motion analysis consists of three steps: 1) define descriptors to represent shape and motion, 2) derive novel indices from the descriptors using statistical modeling; 3) perform LVMD characterization and CRT prediction using a classification approach.

Shape and motion descriptors

The complex LV shape and motion are represented by 4D shape, sphericity, and volume vectors. The AHA 16-segment recommendation (Cerqueira et al., 2002) (Figure 1) is utilized to define 4D shape and volume vectors for each segment and the combined basal, mid-cavity and apical segments.

The LV surface is represented by a mesh that consists of systematically sampled vertices. As shown in Figure 2, 31 uniformly-spaced short-axis slices are selected and each 2D contour is represented by 72 vertices with 5 degree angle increments with respect to the contour's centroid. Concatenating the coordinates of vertices of all cardiac phases forms a *4D shape vector* that contains complete shape and motion information provided by the RT3DE data. The mesh vertices have anatomical correspondence over time and across patients and are referred to as *landmarks*.

The *4D volume vector* is a motion descriptor that contains volumes of LV or its segments for all cardiac phases. Note that the motion patterns contained in the 4D volumes are fully analyzed in the following steps, while only the time to reach minimum volume is considered by the systolic dyssynchrony index (SDI).

The 3D sphericity of LV is defined as

$$\psi = V / (4/3)\pi r^3, \quad (1)$$

where V is the LV volume and r is half the length of the LV major long axis. 3D sphericity has been studied previously and shown to be a sensitive and early marker of post infarction LV remodeling (Mannaerts et al., 2004). The *4D sphericity vector* contains 3D sphericity values of all cardiac phases.

Statistical modeling

Principal component analysis (PCA) (Jolliffe, 1986) is a widely used technique to construct a statistical model of a population containing s samples of n -dimensional vectors $\mathbf{x}_i$. A covariance matrix $\mathbf{C}$ is computed as

$$\mathbf{C} = \frac{1}{s-1} \sum_{i=1}^s (\mathbf{x}_i - \bar{\mathbf{x}})(\mathbf{x}_i - \bar{\mathbf{x}})^T, \quad (2)$$

$$\text{where } \bar{\mathbf{x}} = \frac{1}{s} \sum_{i=1}^s \mathbf{x}_i \quad (3)$$

is referred to as the mean vector. Eigen decomposition of $\mathbf{C}$ identifies eigenvectors ϕ_i that constitute an orthogonal basis. The corresponding eigenvalues λ_i (sorted so that $\lambda_i \geq \lambda_{i+1}$) indicate the variance of the population along the basis. The number of non-zero eigenvalues is $\min(s, n)$. We can retain m eigenvalues and approximate any vector $\mathbf{x}$ in the population by

$$\mathbf{x} \approx \bar{\mathbf{x}} + \Phi \mathbf{b}, \quad (4)$$

where $\Phi = [\phi_1 | \dots | \phi_m]$. The m -dimensional vector $\mathbf{b}$, referred to as *PCA scores*, is computed by

$$\mathbf{b} = \Phi^T (\mathbf{x} - \bar{\mathbf{x}}) \quad (5)$$

and it can be used as an alternative representation of $\mathbf{x}$. The dimensionality m is chosen based on a threshold α (e.g. 97%) that satisfies

$$\sum_{i=1}^m \lambda_i \geq \alpha \sum_{i=1}^{\min(s,n)} \lambda_i, \quad (6)$$

such that the residual—the difference between two sides of eqn (4)—can be considered as noise. When eqn (4) is used to approximate a vector that is not in the modeled population, b_i is often restrained to $\pm 3\sqrt{\lambda_i}$ to ensure that the synthesized vector—the right side of eqn (4)—is similar to those in the modeled population.

In this paper, the PCA scores of the corresponding shape and motion descriptors are used as novel 4D indices. They provide a compact distribution-based representation in the context of the modeled population and reduce the impact of small segmentation errors.

Classification of PCA scores

Statistical test— t -test or MANOVA—is often used to test whether two groups exhibit significant difference in the distributions of certain indices. For example, it can be used to identify the LV segments on which the CRT responders and non-responders exhibit different shape and motion patterns. However, it does not reflect the indices' capability in distinguishing two groups due to two reasons. First, two groups with significantly different means still may have overlapped distributions which prevent total separation. Second, the PCA scores are descriptive and *not* discriminative indices thus a PCA score b_i may not be directly used as LVMD or CRT indicator. Our earlier preliminary study (Zhang et al., 2010b) demonstrated that the PCA scores of pre- and post-CRT datasets, as well as of CRT responders and non-responders, have overlapping distributions that cannot be fully separated by a linear method.

To fully assess the classification capability of the derived indices, the support vector machine (SVM) (Cortes and Vapnik, 1995) is employed in this study. An SVM classifier maps the input data, i.e., the PCA scores, to a space of higher or infinite dimensionality on which the decision boundary is a hyperplane that maximizes the margin that separates two groups of data. The mapping is realized by choosing an appropriate kernel function whose optimal parameters are identified by training. The available toolkit LIBSVM (Chang and Lin, 2001) allows to assess and compare the capability of PCA scores derived from different shape and motion descriptors within a single framework.

In addition to t -test and MANOVA, three types of classification task are performed on all derived indices: 1) normal/LVMD classification to test whether the indices can capture LVMD induced features, 2) pre/post-CRT classification to test whether the indices can track the reverse remodeling process, 3) CRT responder/non-responder classification as CRT outcome prediction test. The performance of these two-class classifications is measured by *classification rate* of any individual class and the overall *accuracy*.

RT3DE Segmentation

The statistical model of shape vectors is utilized in the active shape model (ASM) segmentation method (Cootes and Taylor, 1992): the landmarks of the target shape are iteratively refined and then constrained based on the modeled shape features. The traditional ASM updates each landmark independently along the corresponding scan line based on sampled intensity information, but it can be easily disturbed by noise and neighboring nontarget objects. More sophisticated methods (van Assen et al., 2008; Liu and Udupa, 2009) update all the landmarks simultaneously using intensity information beyond scan lines, but they often are only applicable to low-dimensional data or produce pixel-based results that need to be converted back to landmarks.

The landmark refinement step of ASM segmentation can be implemented by any feature-based segmentation method because it does not directly use the learned shape knowledge. The graph search method (Li et al., 2005, 2006) achieves optimal hyper-surface detection with hard smoothness constraints by constructing a geometric graph from a *presegmented mesh* and computing the minimum s - t graph cut. Within the region considered by the graph, the resulting surface is guaranteed to be globally optimal. In this paper, we use a hybrid method that combines ASM and graph search—using graph search to perform landmark refinement for ASM. Such hybrid method uses the landmarked mesh as the fundamental shape representation, can be easily extended and applied to n -dimensional data, and combines the strengths of learned shape knowledge in ASM and optimal surface detection in graph search.

The graph construction process used for 3D segmentation is illustrated in Figure 3. The graph is built from a presegmented mesh that is close to the target surface and of similar shape. Each mesh vertex corresponds to a landmark of the shape model, through which a *column* of graph nodes is sampled along the surface normal with a certain sampling resolution. A cost function derived from image features associates each node with a cost that indicates the unlikeliness of the target surface passing through the node. The surface segmentation is equivalent to finding an optimal set of nodes, one from each column, with minimum total cost and forming the final surface consisting of these optimal nodes. A hard smoothness constraint is enforced by the inter-column arcs that connect nodes on columns of the same mesh triangle. In Figure 3, a smoothness constraint of one is chosen to ensure that any pair of vertices on the edge of the final surface has a row number (rows 1 to 4 in Figure 3) difference ≤ 1 . The problem of finding the optimal set of nodes can be solved by computing a minimum closed set using the s - t cut algorithm (Li et al., 2005, 2006).

The cost function for RT3DE segmentation is designed as a linear combination of three terms derived from gradient, intensity, and profile patterns. The cost $C(v)$ of a graph node v is

$$C(v) = w_g C_g(v) + w_i C_{i,k}(v) + w_p C_{p,k}(v), \quad (7)$$

where $w_g + w_i + w_p = 1$ and values of $C_*(v)$ are within $[0, 1]$ or $[-1, 1]$ to allow the user to adjust the weights of the terms intuitively to deal with varying image quality. The cost $C(v)$ is computed from a profile vector p (Figure 4) that contains intensity values sampled along the surface normal using the same sampling resolution as the graph construction.

The gradient-based cost $C_g(v)$ is defined as

$$C_g(v) = \begin{cases} 1, & g(v) < 0 \\ \exp(-\frac{g^2(v)}{2\sigma_g^2}), & \text{otherwise} \end{cases}, \quad (8)$$

where $\sigma_g = 20$ and $g(v)$ is the gradient along the surface normal calculated using a Gaussian derivative kernel ($\sigma = 2$).

The intensity-based term $C_{i,k}(v)$ and profile-based term $C_{p,k}(v)$ are designed to incorporate the learned intensity distributions and profile patterns of LV segment k . Let the graph node v in Figure 4 be a landmark of the independent standard, we can use PCA to model the patterns of profile vectors associated with LV segment k . Figure 5 shows the PCA results of LV segment 3. The most significant (first) component is mainly related to the variance of brightness and similar patterns are also observed on other LV segments. Therefore, we can reduce the brightness variation in p by modifying it with

$$\mathbf{p} \leftarrow \mathbf{p} - \phi_1 b_1, \quad (9)$$

where ϕ_1 is the first PCA component and b_1 is the first PCA score. The $C_{i,k}(\mathbf{v})$ and $C_{p,k}(\mathbf{v})$ are computed from the modified $\mathbf{p}$.

It has been shown that the regional intensity information can be incorporated into the optimal graph search (Haeker et al., 2007) as the intensity-based cost $C_{i,k}(\mathbf{v})$: the difference between probabilities of $\mathbf{v}$ belonging to the myocardium, $p_{m,k}(\mathbf{v})$, and blood pool, $p_{b,k}(\mathbf{v})$

$$C_{i,k}(\mathbf{v}) = p_{m,k}(\mathbf{v}) - p_{b,k}(\mathbf{v}), \quad (10)$$

$$p_{m,k}(\mathbf{v}) = \begin{cases} 1.0, & I(\mathbf{v}) > \mu_{m,k} \\ \exp\left(-\frac{(I(\mathbf{v}) - \mu_{m,k})^2}{2\sigma_{m,k}^2}\right), & \text{otherwise} \end{cases}, \quad (11)$$

$$p_{b,k}(\mathbf{v}) = \begin{cases} 1.0, & I(\mathbf{v}) < \mu_{b,k} \\ \exp\left(-\frac{(I(\mathbf{v}) - \mu_{b,k})^2}{2\sigma_{b,k}^2}\right), & \text{otherwise} \end{cases}, \quad (12)$$

where $I(\mathbf{v})$ is the intensity of $\mathbf{v}$, $\mu_{m,k}$ and $\sigma_{m,k}$ are mean and standard deviation of the intensities of myocardium region of LV segment k , $\mu_{b,k}$ and $\sigma_{b,k}$ are of the blood pool. These parameters are determined from profile vectors sampled from the independent standard on which $\mathbf{v}$ in Figure 4 corresponds to the surface voxel; $\mathbf{v} - 3$, $\mathbf{v} - 2$ and $\mathbf{v} - 1$ belong to the blood pool; and $\mathbf{v} + 1$, $\mathbf{v} + 2$ and $\mathbf{v} + 3$ belong to the myocardium.

The profile-based cost $C_{p,k}(\mathbf{v})$ is defined as the difference between two regional probabilities $p_{m,k}(\mathbf{v})$ and $p_{b,k}(\mathbf{v})$. The regional profile vectors $\mathbf{pb}$ and $\mathbf{pm}$ (Figure 4) are used to derive the regional probabilities. All the regional profile vectors of LV segment k sampled from the independent standard are used to construct a statistical model. Let $\mu_{m,k}$ and $\sigma_{m,k}$ be the means and standard deviations of the PCA scores of myocardium profiles, and $\mu_{b,k}$ and $\sigma_{b,k}$ of the PCA scores of blood pool profiles.

$$C_{p,k}(\mathbf{v}) = p_{m,k}(\mathbf{v}) - p_{b,k}(\mathbf{v}), \quad (13)$$

$$p_{m,k}(\mathbf{v}) = \exp\left(-\sum_{j=1}^2 \frac{(b_{m,k,j} - \mu_{m,k,j})^2}{2\sigma_{m,k,j}^2}\right), \quad (14)$$

$$p_{b,k}(\mathbf{v}) = \exp\left(-\sum_{j=1}^2 \frac{(b_{b,k,j} - \mu_{b,k,j})^2}{2\sigma_{b,k,j}^2}\right), \quad (15)$$

where $b_{m,k}$ is the PCA scores of the myocardium profile associated with $\mathbf{v}$ and $b_{b,k}$ is the blood pool PCA scores. The PCA scores associated with the two most significant components are used.

Experimental Methods

Study population

The study protocol was reviewed and approved by the Institutional Review Board of the University of Iowa and informed consent was obtained from all subjects. We recruited 29

retrospective and prospective LVMD patients who were selected for CRT according to the standard clinical indications. The patients were implanted with biventricular pacemaker. Clinical CRT outcome was determined upon post-CRT visit evaluation and was defined as an improvement of at least one functional class as documented by the cardiologist. There were 22 CRT responders, 5 non-responders, and 2 patients with unclear outcome due to non-LVMD complications.

A total of 50 RT3DE datasets were acquired, which included pre- and post-CRT datasets from 21 patients (including all non-responders and patients with unclear outcome), pre-CRT datasets from 7 patients, and post-CRT dataset from 1 patient. Patients were scanned before and/or 1.4–5.3 (2.8 ± 1.1) months after CRT using a Philips Sonos 7500 (Philips Medical Systems, Andover, MA, USA) Live RT3DE machine equipped with an X4 matrix array transducer with 2–4 MHz center frequency to obtain a pyramidal volume in real time. The 3D data sizes were $160 \times 144 \times 208$ with an average resolution of $1.43 \times 1.45 \times 0.92$ mm, the anisotropic voxels had a constant size ratio of 1:1.02:0.65. The number of phases acquired per cardiac cycle was between 10 and 22 (15.0 ± 2.7).

For disease characterization in the context of normal subjects, 35 16-phase 4D MR datasets of 25 normal subjects acquired for a previous study (Zhang et al., 2010c) were used as reference.

Independent standard and image quality

A custom-designed application (Figure 6) was developed to perform reorientation and manual tracing of the RT3DE data. The RT3DE data was first reoriented according to the AHA recommendation (Cerqueira et al., 2002) such that the *XY*-planes corresponded to the short-axis slices, the *XZ*-planes corresponded to four-chamber slices, and the long axis of the heart was orthogonal to the short-axis slices. The LV borders were traced on user selected short-axis slices (locations indicated by the dashed lines on *XZ*- and *YZ*-planes in Figure 6) and the LV volumes were created with distance-based shape interpolation. The LV volume curve of the cardiac cycle and cine movie capability provided extra feedback regarding the tracing quality. The 4D MR datasets were also traced by this application. All datasets were traced by a cardiologist who spent four to six hours on each 4D dataset to produce accurate and smooth shape and motion.

The image quality of RT3DE datasets was evaluated for the entire LV and individual LV segments by the contrast-to-noise ratio (CNR)

$$CNR = (\mu_m - \mu_b) / \sigma_b, \quad (16)$$

where μ_b and σ_b are the mean and standard deviation of the intensities of the blood pool voxels on the first phase of the cardiac cycle, μ_m is the mean intensity of the myocardium region—voxels whose distance from the LV endocardial surface was less than 8 v-units (a voxel with size $1.00 \times 1.02 \times 0.65$ mm).

Shape and motion analysis

The systolic dyssynchrony index (SDI) and 3D sphericity at end-systole (ψ_{ES}) were directly computed from the manual or computer segmentation result. The segmentation of 4D datasets with various numbers of phases per cardiac cycle were normalized to 16 phases per cardiac cycle using distance-based shape interpolation, from which 4D sphericity indices (ψ_{4D}), volumes and shapes were computed. The 4D volumes of each LV segment were also normalized with respect to the LV end-diastolic volume. The 4D volumes of all segments were also concatenated to form a *combined* (with length of 256) 4D volume.

A 4D shape model of the whole LV was first constructed. The translation and scaling that aligned a complete LV shape to the mean shape were also applied to all LV segments when constructing the shape models for individual LV segments. Note that the shape and motion analysis uses the shape vectors defined in the isotropic physical space.

The difference of the target groups in the distribution of indices was tested by t -test or one-way MANOVA such that $p < 0.05$ indicates a significant difference. The indices with low dimensionality, SDI, ψ_{ES} , and combined [SDI, ψ_{ES}] were directly used as input to the SVM classifiers. For high-dimensional indices, ψ_{4D} , 4D volumes and shapes, their corresponding PCA scores were computed and used as the input to SVM classifiers. For normal/LVMD classification, normal datasets and LVMD datasets were used to derive PCA scores. For LVMD classifications, only LVMD datasets were used to derive PCA scores. The pre/post-CRT classification was performed on all 50 LVMD datasets while the CRT responder/non-responder classification was performed on the pre-CRT datasets of 19 patients who had clear CRT outcomes (14 responders, 5 non-responders), for which post-CRT data were available.

The SVM classifiers used the RBF (radial basic function) kernel, whose parameters were identified by a grid search (Chang and Lin, 2001). All classification tasks were performed using *leave-one-out* cross-validation, a generally accepted technique to utilize all available data while guarding against testing hypotheses suggested by the data.

RT3DE segmentation

In general, the hybrid segmentation method is applicable to 4D data such that the 3D images of all phases are segmented simultaneously. However, the 4D approach has certain limitations. First, building a 4D model requires normalization of the number of phases per cardiac cycle, which might remove some important disease related motion information. Second, the motion patterns embedded in a 4D model could introduce biased motion pattern into the segmentation and also might be too stringent. To prevent the modeled motion patterns from affecting segmentation performance, in this paper, the RT3DE datasets were segmented in a 3D phase-by-phase fashion using a two-stage approach implemented by the developed application with graphical user interface (GUI) as shown in Figure 7. Note that because the RT3DE datasets have anisotropic voxels with constant size ratio of 1:1.02:0.65, the shape model used for segmentation was constructed from shape vectors defined in the anisotropic voxel space.

Stage 1: Shape and motion approximation achieves an initial estimate of the LV on all cardiac phases by searching a large region with simple cost.

1. Manually specify the approximate location and size of the LV (shown with yellow dashed lines in Figure 7) and the approximate range of basal motion (ES and ED in Figure 7).
2. Align the 3D mean shape to the first phase of the target data using information provided by step 1.
3. Perform optimal graph search segmentation.
4. Apply modal and basal motion constraints.
5. Align mean shape to the next and/or previous phase(s) using translation and scaling found in step 4 and go to step 3. Note that the last phase is used as the previous phase of the first phase.

The default graph search settings of this stage were: 20 nodes per graph column, sampling resolution of 1 v-unit, smoothness constraint of 2, only gradient-based cost was employed.

The basal motion constraint is that the base must be within ES-5mm and ED+5mm and it is mainly used to increase the robustness of stage 1.

Stage 2: Accurate segmentation was performed on each phase of the target data independently and iteratively. The result of stage 1 was used as the presegmented mesh for the first iteration. The hybrid segmentation was performed with four iterations. The result of each iteration was used as the presegmented mesh for the next iteration, where the graph columns were re-sampled based on the updated mesh. The default graph settings of this stage were: 10 nodes per graph column, sampling resolution of 1 v-unit, smoothness constraint of 2. The three weights of the cost function were specified by the user. Note that there is no basal motion constraint in this stage.

Two cardiologists performed the segmentation independently using the developed GUI based application without knowing the independent standard. The user can check the results of stage 1 and make appropriate adjustments to the manual initialization. Three sets of cost weights can be adjusted in stage 2 where the corresponding results (shown as red, green blue volume curves in Figure 7 which correspond to $w_g=1$, $w_f=1$, and $w_p=1$, respectively) are displayed simultaneously. Such mechanism makes adjusting weights and choosing optimal weights simple and intuitive.

A *5-fold cross-validation* strategy was used to assess the performance of the segmentation. Our 50 RT3DE datasets were divided into five groups of 10 datasets, the pre- and post-CRT datasets of a patient were always put into the same group. The datasets in any group were segmented using models and cost function parameters trained from datasets in the other four groups. The training sets of 40 RT3DE datasets therefore contained 593–620 3D images and corresponding shapes. The final results of stage 2 (chosen by the user) were converted to *binary images* and were compared with those of the independent standard.

Let I and C represent the independent standard and computer segmentation respectively. On each phase, the following measures were computed for the whole LV and the individual LV segments.

1. Signed and absolute average surface positioning errors were computed in millimeters using 3D distance transform (Maurer et al., 2003). If a C surface voxel is positioned inside of the I surface, the signed error is negative.
2. Base and apex offsets were computed as the differences between the z coordinates (approximately along the LV long axis) of the base/apex identified by I and C . Negative offset indicates an underestimation of the length of the LV long axis.
3. Percent overlap of binary volumes

$$overlap\% = 100\% \cdot 2|C \cap I| / (|C| + |I|). \quad (17)$$

4. Percent difference LV volume in milliliter

$$diff\% = 100\% \cdot 2(C - I) / (C + I). \quad (18)$$

The final test of the segmentation accuracy was performed in the context of disease characterization. The indices used for shape and motion analysis were computed from the segmentation results and their corresponding PCA scores were computed with respect to the models constructed using the independent standard. The same set of classification tasks as described for shape and motion analysis was performed on these indices derived from the segmentation results.

Results

LVMD Characterization and CRT Outcome Prediction

Figure 8 shows the relationships between varying PCA scores and changes in the 4D volume of a LV segment. The strongest PCA component is mostly related to the relative size of a segment, the second component is mostly related to the timing of the maximal contraction, and the third component is partially related to the ejection fraction of the segment.

The shape variations introduced by varying the first PCA score of the 4D LV shape model are shown in Figure 9. The most obvious shape variation is in the size of the short-axis cross sections. It also contains secondary variations such as additional bulging or shrinking in the short-axis cross sections of the mid-ventricle and the embedded general LV motion pattern.

For normal/LVMD analyses, the statistical tests showed significant ($p < 0.05$) difference between the groups in all tested indices. The classification using solely the SDI index achieved correctnesses of 0.69 (69%) for normal subjects and 0.68 for LVMD patients with an overall accuracy of 0.68. Classification tests using the other indices invariably achieved almost total normal/LVMD separation with 1.00 ± 0.01 correctness. The results of pre/post-CRT and CRT responder/non-responders analyses are listed in Table 1, the following observations can be summarized.

1. For pre/post analyses of SDI, sphericity and 4D volumes, statistical tests showed no clear distinction between the two groups and the classification accuracies were 0.54–0.72. These are expected because CRT non-responders are included and the responders may not exhibit obvious reverse remodeling yet when the post-CRT data were acquired after 1.4–5.3 (2.8 ± 1.1) months of CRT.
2. For pre/post analyses of 4D shapes, statistical tests showed differences in the PCA scores of 4 basal segments and the whole LV. Better classification accuracies (0.68–0.88) were achieved than the other indices. These findings suggest the existence of subtle shape and motion changes before the effects of the reverse remodeling are reflected in the other indices.
3. For responder/non-responder analyses, statistical tests showed clear distinction between the groups in 4D sphericity and 4D shapes of 9 segments and the whole LV. Most indices have the potential for correct CRT outcome prediction although the prediction rates for non-responders were not high. Predictions using 4D shapes and sphericity demonstrated better performances than when other indices are used.
4. The single-value index, SDI or Ψ_{ES} , exhibited a worse performance than the others.
5. Different LV segments were associated with different classification outcomes. The apical segments (13–16) often corresponded to slightly worse performances than the others.

RT3DE segmentation

Given an initialization and a set of parameters, on a PC equipped with Intel Core i7 processor and running on a single thread, stage 1 of the computer segmentation only takes less than 2 seconds and stage 2 takes 10–15 seconds to produce results from three sets of weights, about 60% of the running time was spent on file I/O and converting graph to binary images. The users were often able to reach the final segmentation after repeating stage 2 for 3–4 times with 9–12 sets of manually specified cost weights tested. The total time spent on a RT3DE dataset (including manual initialization and visual inspection of stage 2 results) was about 5 minutes. Several examples of the achieved segmentations are shown in Figure 10.

The distributions (mean and standard deviation, $\mu \pm \sigma$) of the positioning errors and offsets are listed in Table 2. The means of the signed errors and offsets indicate very small biases. The segmentation inaccuracy is mostly reflected in the absolute errors with means of 2.6–3.9 mm. The difference between the two users is very small in the absolute errors and base offset and is less than 0.5 mm in the means of signed errors. The difference in user initialization is mainly reflected in the apex offset.

The agreement between volumes (binary and milliliter) of manual tracing and computer segmentation is listed in Table 3. The whole LV, basal and mid-cavity segments give slopes that are close to 1 and exhibit good correlations in linear regressions. The variation of segmentation accuracy is mainly reflected in the standard deviations of percent difference and means of the percent overlap. The difference between two users mainly exists in the volume difference and it reflects the different criteria used by the users in choosing the best results. Note that the segmentation results of both users went through all the consequent segmentation accuracy analyses and the results showed no clear difference between the users. Due to limited length of this paper, we only show the analysis results on user 1 here after.

The RT3DE datasets used in this study exhibit large variation in image quality. The distribution of 800 (16 segments, 50 datasets) segmental CNRs are plotted in Figure 11 with respect to individual dataset (Figure 11(a1)) and individual segment (Figure 11(a2)). The datasets are sorted with ascending CNRs of the entire LV and those shown in Figure 10 are datasets 1, 10, 20, 30, 40 and 50. The distributions of corresponding segmental absolute surface positioning errors are shown in Figure 11(b1,b2).

Although Figure 11 suggests that lower image quality often leads to larger positioning errors, linear regression of segmental positioning error and CNR showed no strong correlation ($R=-0.43$). We then sorted and divided the 800 CNR values into four groups, each containing 25% of the data, and computed the median of CNR and the probability of achieving positioning errors less than 3 mm for each group and found a strong correlation ($R=0.97$) between the CNR medians and the probability of errors. It shows that the CNR can be used to estimate the reliability of the computer segmentation. Using the same method as described for image quality of the independent standard, we measured the CNR values from the computer segmentation and tested their correlation with those from the independent standard. The resulting linear regression equation is $y=0.9x+0.11$ with $R=0.92$, which shows that reliable CNR measures can be obtained from the computer segmentation.

The capability of the segmentation in tracking cardiac motion was assessed by temporal errors shown in Figure 12. Since the RT3DE datasets have various numbers of phases, 11 phases with approximately equal percentage time increments (nearest neighbor) were selected to represent the entire cardiac cycle. For most of the errors plotted, their means and standard deviations show no substantial fluctuation within the cardiac cycle. The mean values of mid-cavity volume difference and base offset vary by 8% and 3 mm within the cardiac cycle.

The 4D volume curve is another motion descriptor. The volume curves produced by the independent standard and computer segmentation were compared and several are shown in Figure 13. On four of the datasets shown, the computer segmentations may have consistent over- or under-estimation of the volume but they capture the motion pattern correctly. The irregular motion pattern of dataset 40 is also mostly captured in the computer segmentation.

For normal/LVMD analyses using indices derived from the computer segmentations of the LVMD data, the statistical tests showed significant ($p<0.05$) difference between the groups in all tested indices. The classification of SDI achieved correctnesses of 0.97 for normal and

0.80 for LVMD and an overall accuracy of 0.87. The additional classifications using remaining indices achieved correctnesses of 0.98 ± 0.04 for normal and 0.99 ± 0.02 for LVMD and an overall accuracy of 0.99 ± 0.02 , which are very similar to those achieved using indices derived directly from the independent standard. The results of pre/post-CRT and CRT responder/non-responders analyses are listed in Table 4. When comparing with the results listed in Table 1, the following observations can be presented:

1. Most observations stated for Table 1 remain valid for results seen in Table 4.
2. Only one LV segments showed different distribution of shape PCA scores in the pre/post analyses.
3. The LV segments with different distribution of shape PCA scores in the CRT prediction analyses are slightly different from those in Table 1.
4. Classifications of indices derived from the computer segmentations often have lower classification rates than those from the independent standard.
5. Among the responder/non-responder classifications, those using 4D shapes exhibit less performance decline than using the other indices.

Discussion

Traditional clinical approaches of disease characterization are frequently deriving a single-value index with physiological meaning and then testing its capability on a certain population. A capable index should describe the disease feature in a comprehensive manner, be robust to observer variability, and have minimal distribution overlap on the target groups. In practice, it is extremely difficult to find a capable index for LVMD which introduces complex changes to the shape and motion of the heart. In addition, to our knowledge, the possibility of combining multiple less capable indices that describe different aspects of the shape and motion has not been fully explored for LVMD.

Our approach of using PCA and SVM techniques has some unique advantages. First, indices with high dimensionality are identified by PCA that fully utilizes the knowledge about the population embedded in the input data which can assume any form and combination of available information. Second, we showed that the more information is used the less the final classification is sensitive to observer variability (Tables 1 and 4). Third, the SVM can maximize the separation of the two target classes via training and feature mapping.

The results of *t*-test and MANOVA are not direct indicators of but are compatible with the classification performances. As seen in Table 1, the statistical tests showed that the difference between pre- and post-CRT groups is more obvious in the 4D shapes than in 4D volumes, which are compatible with the pre/post classifications of 4D shapes achieving better accuracies than those of 4D volumes.

The main limitation of the disease characterization in this study is the small study population, especially the number of CRT non-responders that prevents us from reaching conclusive assessment on the prediction power of the derived indices. However, our experiment setup—comprehensive tasks ranging from normal/LVMD to responder/non-responder classifications using a consistent classifier configuration—allow us to demonstrate the potential of the derived indices and compare their capabilities. The 4D shape PCA scores, mainly due to the complete utilization of 4D shape and motion information, show great promise in LVMD characterization and CRT outcome prediction.

The post-CRT datasets were acquired a short period of time ($1.4\text{--}5.3$, 2.8 ± 1.1 months) after the implantation, while the CRT outcomes were determined in later post-CRT visits,

therefore the CRT-responders may not have a clear improvement of LV function reflected in the post-CRT data. Our findings agree with our earlier preliminary reports that there is no statistically significant difference between the pre- and post-CRT datasets as well as between the responders and non-responders in traditional LV functional indices such as ejection fraction, end-diastolic and end-systolic volumes (Gupta et al., 2011). However, we noticed large changes of PCA scores between pre- and post-CRT in some CRT responders (Zhang et al., 2010b) that indicated the potential for tracking changes of the disease status. Such promise was further confirmed in this paper by the comprehensive pre/post-CRT analyses (Table 1), where the basal segments start to show obvious changes in PCA scores and the classification accuracy using PCA scores of the 4D LV shape reached 80%.

The main disadvantage of the PCA+SVM approach currently is, and will continue to be in achieving clinical understanding due to the non-intuitive nature of the components, dependency on the studied population, and understandability of the math involved. However, these techniques will allow us to answer two important questions in the future: Can the CRT outcome be accurately predicted using the available 4D information, and what is the maximal achievable CRT prediction rate given certain amount of information. Used as benchmarks, these comprehensive indices may also help us in find easy-to-use clinical CRT outcome predictors.

The segmentation method in this paper is designed to handle the large variations in image quality that is typical for the RT3DE data. All clinical datasets collected during the study were used in this work, including some low quality images (such as the first dataset shown in Figure 10), which would likely be discarded under the criteria of other reported studies (Corsi et al., 2002; Lin et al., 2003; Crosby et al., 2009). Note that in these datasets, we can still achieve accurate segmentation on several LV segments, which can thus be used for reliable disease characterization. The parameters of the cost function were trained and assigned based on the fact that different LV segments have different distributions of image quality, which was demonstrated in the CNR-segment plot in Figure 11. We have demonstrated that the image quality mainly determines the probability of achieving expected segmentation accuracy and can be used as a confidence indicator.

The user-specified cost weights provide a mechanism to allow the user to fully explore the capability of the segmentation algorithm. The user, with the help of visual feedback, can easily and intuitively determine how to combine the gradient, intensity, and profile pattern information to achieve better result. This simple user interaction also helps to reduce the amount of subsequent manual editing, if it is necessary. In our tests, we noticed that the final weights used on high-CNR datasets have a certain pattern and after segmenting several such datasets the user can process a dataset in 5 minutes or less. The final weights used for low-CNR datasets have no unique pattern because the user often had to balance between several criteria,—better whole LV motion, better accuracy on visible segments, etc.—on different datasets to reach the final result.

Nevertheless, further visual comparison of the independent standard with the computer segmentation showed several limitations of our method.

First, identifying the mitral valve hinge plane that defines the last basal slice is a difficult task for our method because it does not explicitly consider the valve leaflets and their motion and does not utilize 3D/4D context of the left atrium.

Second, the method's robustness to varying image quality, while quite remarkable, is still limited. When several neighboring segments, such as lateral segments 5, 6, 11, 12 and 16, are all almost invisible on the image (such as in the first dataset shown in Figure 10), the manual tracing and computer segmentation take different approaches to estimate the

surfaces using available information. The manual tracing focuses on the consistency of the LV shape and on smooth cardiac motion, while the computer segmentation relies on global and local constraints that are only available in 3D. Therefore, large segmentation errors, which may be considered as observer variability due to insufficient image information, are inevitable in these segments. We found that larger errors often correspond to segments that reside in the middle of several continuous segments with weak image boundary information.

As indicated by the comparison of Tables 1 and 4, the segmentation errors affect the disease characterization and CRT prediction by reducing their performance. Such effects are more apparent when using indices that are mostly related to the milliliter volumes. On the other hand, the 4D shape analyses are less sensitive to these segmentation errors.

Conclusions

In this paper, the characteristics of LVMD are represented by novel 4D descriptors including 4D sphericity, volume, and shape, as well as clinical indices including the systolic dyssynchrony index and end-systolic sphericity. Novel 4D indices (PCA scores) are derived from the 4D descriptors and are assessed by a classification-based approach. The results show that the 4D indices capture unique shape and motion features of LVMD and achieve 100% normal/LVMD classifications, they also have promising capabilities and great potential for tracking the LV reverse remodeling process and improving CRT outcome prediction.

We developed a segmentation method that combines the powers of active shape models and optimal graph search to achieve high efficiency. This method was incorporated into a GUI-based application that provides the user with simple manual initialization, intuitive parameter controls, and visual feedback of segmentation accuracy. The validation results showed that the method achieved very good accuracy and was robust to varying user initialization and image quality. We also demonstrated that the image quality measurement can be used as a performance indicator because it is tied to the probability of achieving a certain segmentation accuracy. Finally, the segmentation performance is assessed in the context of disease characterization, evaluating how the segmentation inaccuracies affect the classification performance. The comparison of classification results show that the PCA scores of 4D shape model are highly suitable for disease characterization and very insensitive to segmentation imperfections.

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1. basal anterior	7. mid anterior	13. apical anterior
2. basal anteroseptal	8. mid anteroseptal	14. apical septal
3. basal inferoseptal	9. mid inferoseptal	15. apical inferior
4. basal inferior	10. mid inferior	16. apical lateral
5. basal inferolateral	11. mid inferolateral	
6. basal anterolateral	12. mid anterolateral	

Figure 1.
Sixteen left ventricular segments.

Figure 2.
Meshes of (a) full LV, (b) apical (#13–16) segments, and (c) basal (#1–6) segments.

Figure 3.
Graph construction.

Figure 4.
The profile vector p associated with graph node v .

Figure 5. Results of PCA on profile vectors of LV segment 3: mean profile (solid lines) and variations associated with four strongest components (dashed lines correspond to $\bar{p} \pm 2\sqrt{\lambda_i}\phi_i$).

Figure 6.
Manual tracing of reoriented RT3DE dataset.

Figure 7. Screenshot of the RT3DE segmentation application. Yellow dashed lines show the user-specified region of interest. Three segmentation results using different sets of cost weights and their corresponding 4D volumes are shown (red: $w_g=1$, green: $w_f=1$, blue: $w_p=1$).

Figure 8.

Variations of 4D volumes of LV segments 3 (a1–a3) and 8 (b1–b3) associated with varying first three PCA scores (top to bottom) by $\pm 2\sigma$ (dashed lines) and the mean volumes (solid lines) of models derived from the independent standard of 50 LVMD datasets.

Figure 9. Shape variations at phases 0 (top row) and 7 (bottom row) introduced by varying the first PCA score of the 4D LV shape model derived from the independent standard of 50 LVMD datasets. The values of the first PCA score are: -2σ (left), 0 (mean shape, middle), and 2σ (right).

Figure 10.

Examples of segmented RT3DE data. Six datasets with increasing image quality measured by CNR for the whole LV are shown, where dataset 1 has the lowest CNR among all 50 datasets tested.

Figure 11.

(a1–2) Distributions ($\mu \pm \sigma$, blue +s' and lines) of image quality (CNR of LV segment) for individual RT3DE dataset (a1) and individual segment (a2). Red line in (a1) shows the *sorted* CNRs of the whole LV. (b1–2) Distributions of absolute positioning errors (measured for each LV segment) for individual RT3DE dataset (b1) and individual LV segment (b2).

Figure 12.

Distributions ($\mu \pm \sigma$) of temporal segmentation errors. (a1–3) absolute positioning errors; (b1–3) percent volume differences; (c1–2) base and apex offsets.

Figure 13.

Comparison of volume curves derived from the manual tracing and computer segmentations of the RT3DE datasets shown in Figure 10.

Table 1

Pre/post and responder/non-responder classification performance using indices derived from the *independent standard*. Bold texts mark the indices on which the two target groups have significantly different distributions indicated by *t*-test or one-way MANOVA with $p < 0.05$.

	Pre	Post	Acc	Rpd	nRpd	Acc	Pre	Post	Acc	Rpd	nRpd	Acc
SDI	1	0.05	0.58	1	0	0.74						
ψ_{ES}	1	0	0.56	0.86	0.40	0.74						
[SDI, ψ_{ES}]	1	0	0.56	0.79	0.20	0.63						
ψ_{4D}	0.71	0.50	0.62	0.93	0.60	0.84						
<i>4D volume PCA</i>												
segment 1	0.89	0.18	0.58	0.79	0.40	0.68	0.75	0.73	0.74	0.93	0.20	0.74
segment 2	1	0	0.56	0.93	0.60	0.84	0.79	0.55	0.68	1	0.80	0.95
segment 3	0.82	0.18	0.54	0.86	0.40	0.74	0.79	0.77	0.78	1	0.80	0.95
segment 4	0.93	0.18	0.60	1	0	0.74	0.93	0.64	0.80	1	0.40	0.84
segment 5	0.93	0.18	0.60	1	0.60	0.89	0.93	0.73	0.84	0.85	0.40	0.74
segment 6	0.57	0.41	0.50	0.86	0.40	0.74	0.89	0.64	0.78	0.93	0.40	0.79
segment 7	0.89	0.32	0.64	1	0	0.74	0.82	0.64	0.74	1	0.80	0.95
segment 8	0.79	0.32	0.58	1	0.80	0.95	0.86	0.82	0.84	1	0.40	0.84
segment 9	0.96	0.41	0.72	0.93	0.80	0.89	0.89	0.45	0.70	1	0.60	0.89
segment 10	0.82	0.27	0.58	1	0	0.74	0.79	0.82	0.80	0.86	0.40	0.74
segment 11	0.71	0.45	0.60	1	0.40	0.84	0.96	0.64	0.82	1	0.40	0.84
segment 12	0.82	0.59	0.72	0.93	0.60	0.84	0.96	0.77	0.88	1	0.40	0.84
segment 13	0.61	0.59	0.60	0.86	0.20	0.68	0.86	0.36	0.64	0.93	0.80	0.89
segment 14	1	0	0.56	1	0	0.74	0.64	0.41	0.54	0.86	0	0.63
segment 15	0.64	0.64	0.64	1	0	0.74	0.68	0.68	0.68	1	0.40	0.84
segment 16	0.75	0.59	0.68	0.93	0.60	0.84	0.82	0.64	0.74	0.93	0.60	0.84
combined	0.71	0.50	0.62	1	0.20	0.79	0.82	0.82	0.82	0.93	0.60	0.84

Table 2Surface positioning errors and offsets ($\mu \pm \sigma$).

	User 1		User 2	
	sgn mm	abs mm	sgn mm	abs mm
<i>Average surface positioning errors</i>				
LV	0.94±1.98	3.20±1.10	0.38±1.85	3.16±0.98
B	0.64±1.78	2.72±1.11	-0.05±1.53	2.63±0.78
M	0.81±2.51	3.25±1.36	0.48±2.26	3.23±1.20
A	1.48±2.32	3.86±1.41	0.86±2.56	3.93±1.52
<i>Offsets</i>				
B	1.26±2.71	2.89±1.49	-0.91±2.53	2.80±1.28
A	1.60±3.00	2.82±1.92	-0.10±5.33	4.23±2.52

LV: whole LV, B: basal segments/base

M: mid-cavity segments, A: apical segments/apex.

Table 3

Results of linear regressions (equation and R), volume differences, and volume overlaps ($\mu \pm \sigma$).

	Linear Regression		diff%	overlap%
	eq. (ml)	R		
<i>User 1</i>				
Whole LV	0.97x+20.4	0.83	4.2±17.4	86.3±4.3
Basal	0.99x+3.3	0.87	1.9±15.7	87.6±4.4
Mid-cavity	0.95x+11.7	0.80	6.3±20.1	88.9±4.4
Apical	0.87x+8.2	0.62	2.7±27.0	78.2±7.2
<i>User 2</i>				
Whole LV	0.95x+11.3	0.84	−1.3±16.8	86.2±3.8
Basal	1.04x−3.7	0.89	−1.4±15.7	87.9±3.3
Mid-cavity	0.90x+10.3	0.80	−0.4±19.2	88.9±3.7
Apical	0.77x+9.6	0.57	−5.1±29.1	76.7±7.9

Table 4

Pre/post and responder/non-responder classification performance using indices derived from *computer segmentations*. Bold texts mark the indices on which the two target groups have significantly different distributions indicated by *t*-test or one-way MANOVA with $p < 0.05$.

	Pre	Post	Acc	Rpd	nRpd	Acc	Pre	Post	Acc	Rpd	nRpd	Acc
S _{DI}	1	0	0.56	1	0	0.74						
ψ_{ES}	1	0	0.56	1	0	0.74						
[S _{DI} , ψ_{ES}]	1	0	0.56	1	0	0.74						
ψ_{4D}	0.64	0.59	0.62	0.93	0.60	0.84						
<i>4D volume PCA</i>												
segment 1	0.64	0.32	0.50	0.86	0.60	0.79	0.82	0.32	0.60	0.93	0.20	0.74
segment 2	0.75	0.36	0.58	0.93	0.20	0.74	0.75	0.64	0.70	1	0.80	0.95
segment 3	0.50	0.45	0.48	0.79	0.60	0.74	0.71	0.64	0.68	1	0.60	0.89
segment 4	0.75	0	0.42	0.93	0.40	0.79	0.75	0.27	0.54	1	0	0.74
segment 5	0.68	0.55	0.62	1	0.20	0.79	0.82	0.50	0.68	0.78	0.60	0.74
segment 6	1	0	0.56	1	0	0.74	0.82	0.55	0.70	1	0.20	0.78
segment 7	0.71	0.05	0.64	1	0	0.74	0.86	0.55	0.72	0.79	0.40	0.68
segment 8	0.79	0.45	0.64	0.93	0.20	0.74	0.89	0.32	0.64	0.79	0.60	0.74
segment 9	0.64	0.64	0.54	0.93	0.60	0.84	0.75	0.68	0.72	0.86	0.60	0.79
segment 10	0.64	0.45	0.56	1	0	0.74	0.61	0.77	0.68	1	0.60	0.89
segment 11	0.79	0.55	0.68	0.93	0.20	0.74	0.79	0.18	0.52	0.79	0.60	0.74
segment 12	1	0	0.56	0.86	0.80	0.84	0.71	0.50	0.62	1	0	0.74
segment 13	.71	0.59	0.66	0.93	0.20	0.74	0.82	0.59	0.72	0.79	0.60	0.74
segment 14	0.57	0.18	0.40	1	0	0.74	0.75	0.64	0.70	1	0.80	0.94
segment 15	0.79	0.41	0.62	0.93	0.40	0.79	0.79	0.45	0.64	0.86	0.60	0.79
segment 16	0.79	0.32	0.58	1	0	0.74	0.86	0.45	0.68	0.93	0.60	0.84
combined	0.79	0.45	0.64	0.93	0.40	0.79	0.68	0.73	0.70	1	0.20	0.79