NOVEL METHODOLGY FOR QUANTIFYING LEFT-VENTRICULAR DYSSYNCHRONY FROM CARDIAC MRI USING PRINCIPAL COMPONENT ANALYSIS

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Abstract

Introduction: Cardiac resynchronization therapy (CRT), which restores normal electrical conduction to the heart, is very effective for selected patients with systolic heart failure, particularly those with regional variations in left-ventricular (LV) motion, also known as LV dyssynchrony. Unfortunately, CRT is associated with a 30-40% non-response rate due to sub-optimal patient selection based solely on cardiac electrophysiological criteria rather than measures of mechanical LV dyssynchrony.

Imaging can be used to non-invasively track LV mechanics but current imaging-based measures of LV dyssynchrony using echocardiography are subjective and ineffective at significantly lowering the CRT response rate. Cardiac Magnetic Resonance (CMR) imaging provides high SNR, high-resolution circumferential, radial and longitudinal strain data throughout the cardiac cycle and hence is a suitable imaging modality for quantifying LV dyssynchrony in heart failure patients. In particular, the CMR method known as 2D cine displacement encoding with stimulated echoes (DENSE) accurately measures regional ventricular strain in 2D short-axis and long-axis planes from phase images of LV displacement.

The current gold standard for quantifying LV dyssynchrony using 2D cine DENSE MRI is known as the circumferential uniformity ratio estimate (CURE) which is calculated from circumferential LV strains. Unfortunately CURE has the limitation that it is calculated from Fourier series fitting of LV strains and needs to be averaged over different cardiac frames resulting in possible LV strain distortions, user subjectivity and time dependence.

Methods: To overcome the limitations of current measures of LV dyssynchrony, new time-independent, user-independent, data-driven metrics of LV dyssynchrony have been developed and tested in a canine model of heart failure using a 24-segment model of the LV. Basal, mid-ventricular and apical short-axis images of LV motion over the cardiac cycle, acquired using 2D cine DENSE MRI, were used to calculate LV dyssynchrony metrics from LV strains. These metrics are known as first-order regional conformity estimate (FORCE) and First Order Regional Metric of Estimated Disparity (FORMED). FORCE and FORMED quantify regional dyssynchrony in LV motion by decomposing LV strains into principal components over space and time respectively.

Results: FORCE, FORMED and CURE were found to be significantly different in canines with LV dyssynchrony compared to those with LV synchrony in the case of circumferential strains but not in the case of radial strains. In a preliminary analysis of a 23-patient subset of 70 CRT patients where a reduction in LV end-systolic volume of >=15% indicated positive response, cutoffs of CURE<0.7, FORCE< 0.795 and FORMED>0.9 indicated LV dyssynchrony. For these cutoffs, CURE, FORCE and FORMED had specificities (true negative rate) of 0.714, 0.714, 0.429 (sensitivity or true positive rate=1 for all metrics) respectively indicating that FORCE was the best metric for CRT patient selection.

Conclusions: FORCE and FORMED are effective metrics of LV dyssynchrony in canine models of heart failure and FORCE is ideal for selection of heart failure patients for CRT. Improvements in FORCE and FORMED, such as the use of higher order principal components, could further improve the ability of these metrics to improve patient selection and hence improve patient outcome in CRT trials for heart failure patients.

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CHAPTER 1-LV DYSSYNCHRONY IN THE CONTEXT OF HEART FAILURE THERAPIES

1.1 Importance of heart failure

Cardiovascular disease remains the No. 1 cause of death globally despite declining mortality from heart disease. To illustrate the severity of cardiovascular diseases, 17.3 million people have been estimated to have died from cardiovascular diseases in 2008, which represents 30% of all global deaths [1]. Cardiovascular deaths fall roughly into two different categories: sudden cardiac death or heart failure [2]. The focus of this work is on improving the effectiveness of heart failure therapies. Given that approximately 5.7 million Americans were diagnosed with congestive heart failure in 2009 with half of them having systolic dysfunction, diagnosis of regional dyssynchronous ventricular contraction is of high clinical importance. In this study, accurate non-invasive imaging-based measures of LV dyssynchrony are being explored, although RV and inter-ventricular dyssynchrony are also important in other clinical contexts.

1.2 Treatment of LV dyssynchrony

1.2.a. Pathophysiology of LV dyssynchrony

In normal hearts, electrical impulses pass from the atrio-ventricular (AV) node to the interventricular septum and then the ventricles through a bundle of cardiac fibers known as the bundle of His. In left bundle branch block (LBBB), conduction through the bundle of His is impaired resulting in contraction of septum and lateral wall stretch of the LV during early systole and vice-versa during late systole [3]. This results in a nonhomogeneous and delayed

depolarization of the left ventricle [4]. Asynchronous ventricular activation during LBBB leads to redistribution of circumferential shortening and myocardial blood flow and, in the long run, left ventricular remodeling [5]. LBBB in patients can reduce global LV ejection fraction, cardiac output, mean arterial pressure, etc. [6]

1.2.b. Cardiac Resynchronization Therapy (CRT)

A treatment method known as cardiac resynchronization therapy, commonly known as CRT, can restore normal electrical conduction of the heart through the use of a device known as an implantable cardioverter-defibrilator (ICD). ICD devices in the context of CRT typically contain pacing leads for the right ventricle, the right atrium, and the left ventricle (via the coronary sinus) i.e. bi-ventricular pacing, similar to the leads of a pacemaker [2].

Electrical resynchronization can reduce the LBBB-induced mechanical interventricular dyssynchrony between the right and the left ventricle and the intraventricular dyssynchrony within the left ventricle. Minimizing intraventricular dyssynchrony has been shown to improve global LV function; that is CRT increases LV filling time, decreases septal dyskinesis, and reduces mitral regurgitation, thus improving hemodynamics [6].

Selection of patients with systolic heart failure for treatment by CRT according to the 2008 American College of Cardiology /American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines was associated with significant nonresponse rates [7]. Hence, the most recent 2012/2013 CRT guidelines now emphasize selecting patients using the surface

electrocardiogram (ECG) to characterize bundle branch block morphology and the extent of QRS widening [8,9].

1.3 Drawbacks of current measures of LV dyssynchrony

1.3.a. Electrophysiological criteria

The drawback of using ECG criteria to identify optimal CRT candidates is that there is a large amount of variability in the amount of mechanical dyssynchrony and scar within groups of patients with the same ECG phenotypes. However, attempts to use imaging-based LV dyssynchrony parameters using echocardiography produced suboptimal patient selection for CRT in the Predictors of Response to CRT (PROSPECT) clinical trial [10,11].

1.3.b. Imaging criteria

Fortunately, recent studies based on innovative characterization of mechanical dyssynchrony by Fourier transformation (FT) of regional strain from cardiac MRI have been very promising for identifying CRT response [12]. This approach, based on identifying regional non-uniformities in cardiac contraction, has previously been determined to be superior to more traditional analyses of mechanical dyssynchrony relying on regional differences in time to peak strain [13].

1.4. Purpose of improved metrics of LV dyssynchrony

In the present analysis, the results of two further improved approaches to quantifying LV dyssynchrony from cine DENSE MRI strain data based on principal component analysis (PCA)

are compared to current LV dyssynchrony metrics such as CURE. PCA has previously been used to determine mechanical dyssynchrony, but has not been applied directly on CMR strain data (without any prior training data) to distinguish dyssynchronous and synchronous LV contraction [14]. Like FT analysis, PCA also does not require determination of regional differences in time to peak strain. Nevertheless, PCA represents a potential improvement over FT analysis because it is completely data-driven without any assumed form of the strain function and also characterizes the data in global form without the need for time averaging. A time-independent, data-driven measure of LV regional dyssynchrony is important to minimize subjectivity in dyssynchrony quantification which is crucial to CRT patient selection since LV dyssynchrony is currently being identified by hard thresholding of suitable imaging parameters.

CHAPTER 2- QUANTIFICATION OF LV DYSSYNCHRONY USING PRINCIPAL COMPONENT ANALYSIS (PCA)

The following imaging studies in this chapter which include construction of an animal model of LV dyssynchrony, LV strain estimation for canines, cine DENSE MRI for patient and canine studies and other clinical MRI methods for patient studies were performed by Dr. Bilchick. These studies involved the comparison of PCA-based metrics with CURE. My contributions included calculation of LV strains of CRT patients, quantification of LV dyssynchrony using FORCE, FORMED and CURE in canine and patient studies and statistical analyses of all HF patients referred for CRT.

2.1 Animal model of LV dyssynchrony

Animal model

Canine models of dyssynchronous (N=5) and synchronous (N=5) heart failure (HF) were studied in addition to normal canines (N=4). Sample sizes were determined by power analysis with desired power (1-β) =90% and desired type I error α=5%. For dyssynchronous HF, a left bundle branch block (LBBB) method was used [15]. As previously described in [13], heart failure was induced in a total of 10 canines with right atrial tachy-pacing at 180 beats/min. for 5 weeks. In order to induce dyssynchronous HF, left bundle branch ablation was performed (50 W, temperature<=60^{o}) before tachycardia pacing (LBBB-HF) with a 4 mm-tip ablation catheter in 5 canines which widened the QRS duration from 55-60 ms to approximately 120 ms. Persistence of LBBB was confirmed after a 30 minute waiting period and at the time of the final MRI exam.

The other 5 canines did not undergo left bundle branch ablation, had narrow QRS (NQRS) durations of 55-60 ms and were models of synchronous HF (NQRS-HF). Four normal canines did not undergo ablation or tachy-pacing and formed the additional control group to account for the effect of tachy-pacing on the synchrony of LV contraction. This study was approved by the University of Virginia Animal Care and Use Committee (ACUC) [13].

2.2 cine DENSE MRI of LV motion and estimation of LV strains

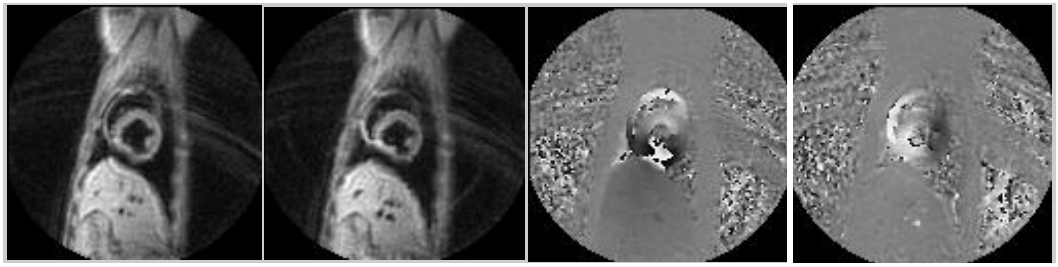
Imaging methods for quantifying LV dyssynchrony in canines

Spiral cine Displacement ENcoding with Stimulated Echoes (DENSE) imaging [13] was performed on a 1.5 T Avanto scanner (Siemens Medical Solutions, Erlanger, Germany) with a 4-channel phased-array radiofrequency coil in all 14 canines. Short-axis and long-axis planes from cine DENSE images were acquired using the following parameters for each plane: interleaved spiral readout with 6 interleaves/image, repetition time (TR)=17 ms, echo time (TE)=1.9 ms, field of view=350-by-350 mm, slice thickness=8 mm, excitation flip angle=15°, in-plane resolution=2.8 x2.8 mm, echo spacing (temporal resolution)=17 ms with view sharing and displacement-encoding frequency= 0.1 cycles/mm. Fat suppression was also used to nullify the signal from fat and improve image quality [16,17]. 2D cine DENSE encodes myocardial displacement in the phase of the images [18] so that myocardial strain is calculated from the phase, rather than the magnitude images as described below. The magnitude and phase images

acquired in different directions for sample NQRS-HF, Normal and LBBB-HF canines are shown below in Figure 2-1 A,B and C.

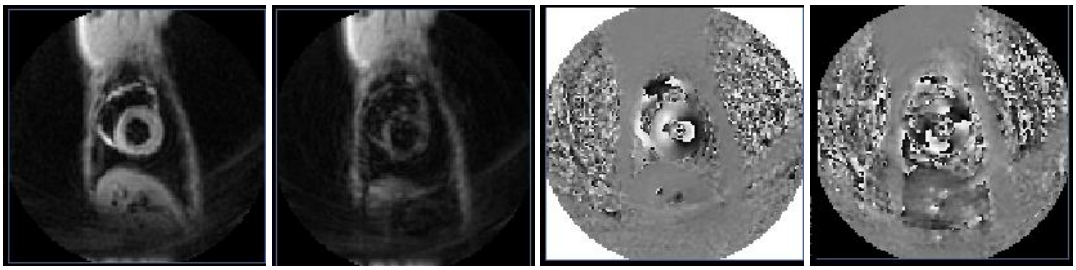
A) End-systole-Sample NQRS canine

$X_{magnitude}$ $Y_{magnitude}$ X_{phase} Y_{phase}



B) End-systole-Sample Normal canine

$X_{magnitude}$ $Y_{magnitude}$ X_{phase} Y_{phase}



C) End-systole-Sample LBBB canine

$X_{magnitude}$ $Y_{magnitude}$ X_{phase} Y_{phase}

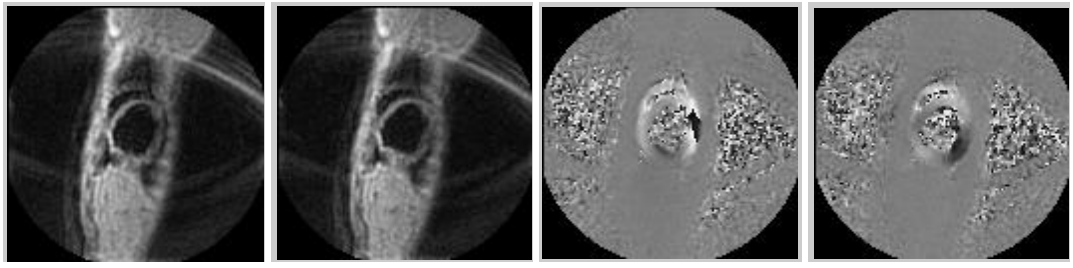


Figure 2-1: cine DENSE MR images (x-magnitude, y-magnitude, x-phase and y-phase) of LV motion at end-systole in sample A) NQRS-HF (top row), B) Normal (middle row) and B) LBBB-HF (bottom row) canines.

Image analysis for calculation of myocardial strains

After image acquisition, segmentation of the left ventricular (LV) myocardium was performed. First, a process known as motion guided segmentation was used to propagate epicardial and endocardial LV contours along the cardiac cycle starting from the initial contour [19]. Next, a quality-guided phase unwrapping algorithm was used to obtain accurate phase values in the traced myocardial region from x- and y-phase images. This algorithm utilizes a technique known as phase unwrapping to extract the actual phase from the phase acquired using the MR scanner which is "wrapped" to the interval $[-\pi, \pi]$. From these phase values, myocardial displacements were calculated. Lagrangian strain was computed from these displacements in 24 LV segments in multiple short-axis 2D slices in radial (E_{rr}) and circumferential directions (E_{cc}). Strains were reported as the mean of strain values over all segment pixels. Strains were calculated from cine DENSE images with an algorithm developed in Matlab (MathWorks, Natick, Massachusetts) according to the procedure mentioned above [18]. Figure 2-2 A, B and C show the displacement maps calculated for the same sample NQRS-HF, Normal and LBBB-HF canines shown in the previous figure.

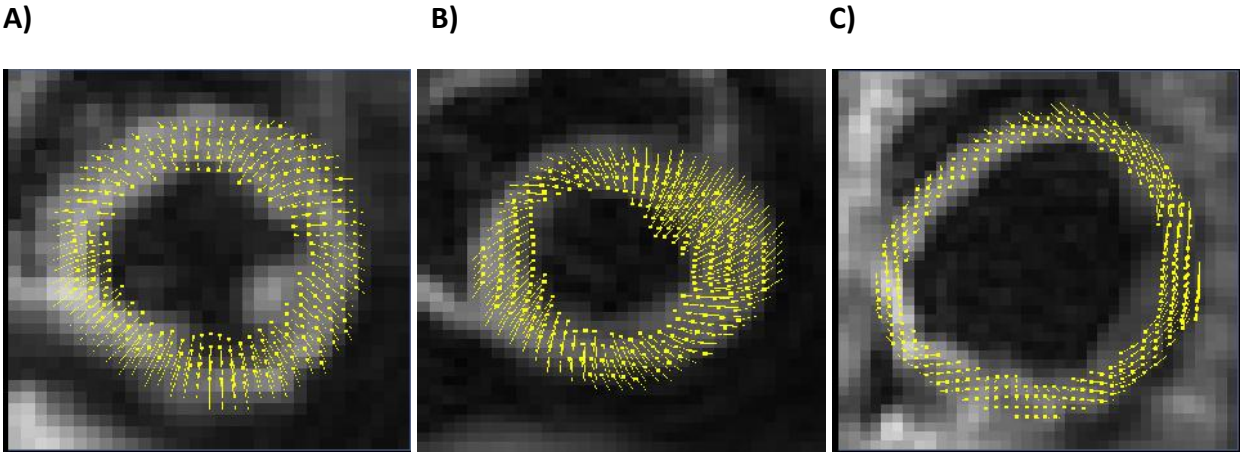


Figure 2-2: MR images of regional LV displacement at end-systole in sample A) NQRS-HF, B) Normal and C) LBBB-HF canines. Note the heterogeneity for the LBBB-HF canine and uniformity for NQRS-HF and Normal canines in regional displacement.

2.3 PCA decompositions of LV strains

Model of LV regional strain calculations

Since midwall myocardial fiber orientation is typically circumferential, analysis of LV dyssynchrony using midwall E_{cc} in a short-axis plane was preferred [20]. The mid-ventricular and basal short-axis slices were captured for all canines and hence these slices were used for the calculation of LV dyssynchrony. The purpose of using multiple short-axis slices was to observe effects of slice location on calculation of LV dyssynchrony in order to optimize slice analyses for CRT patient studies of LV dyssynchrony. LV dyssynchrony measures based on radial strains (E_{rr}) have also been calculated for comparison with E_{cc}-based LV dyssynchrony since current echocardiographic-based measures of LV dyssynchrony are based on E_{rr}. 24 short-axis cardiac segments were used to compute regional Lagrangian strains for each cardiac phase, where the

six main sectors of the LV (Anterior, Antero-Lateral, Infero-Lateral, Lateral, Infero-Septal and Antero-Septal) are each divided into four equal segments.

Application of principal component analysis to mechanical dyssynchrony

The LV E_{cc} or E_{rr} values calculated from the analysis of cine DENSE images were stored in the matrix X with dimensions equal to no. of cardiac phases (M) x no. of LV segments (N). Principal component analysis of LV strains involves the expression of X in terms of basis functions over time and space. Typically, X is centered about its column means but this step would distort the LV strain-time curves and deprive them of their physiological meaning ($E_{cc}(t=0)$ and $E_{rr}(t=0)$ are zero during LV contraction and relaxation since no displacement has occurred at t=0) and so this step is omitted. Consequently, uncentered (non-mean-subtracted) PCA was performed on the LV strains to identify spatio-temporal relations between strains. These basis functions over space and time are termed principal component loadings (PCLs) which are axes of an orthonormal coordinate system that represents the variation in the data along a fixed dimension, i.e time or space for LV strains [21]. The process of decomposing X into its PCLs is known as singular value decomposition (SVD). The SVD of X is shown below [21]:

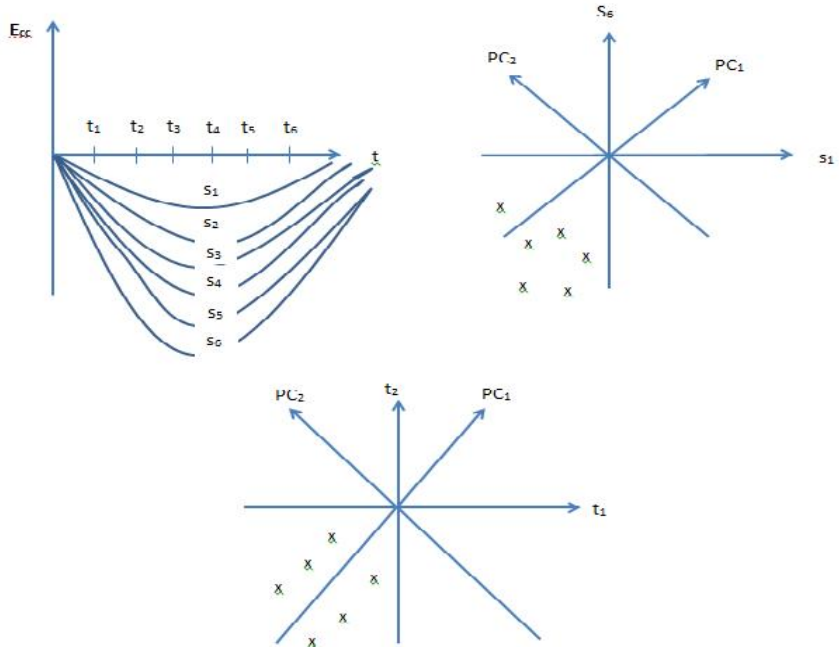
Equation 1: $$X = USV^T$$

where $U=[u_1\ u_2 \dots u_M]$, $S = \begin{bmatrix} s_1 & 0 & 0 & \dots & 0 \\ 0 & s_2 & 0 & \ddots & 0 \\ 0 & 0 & s_3 & \ddots & 0 \\ \vdots & \vdots & \vdots & \ddots & 0 \\ 0 & 0 & 0 & \dots & s_{\min(M,N)} \end{bmatrix}$, and $V=[v_1\ v_2 \dots v_N]$

Of note, u_i for i=1,2,…,M and v_j for j=1,2,…,N are column vectors denoting PCLs over space and

time respectively. S is a diagonal matrix containing the singular values of matrix X which are scaling factors representing the contribution of each principal component to the total variation in LV strains. U and V are orthonormal matrices meaning that the rows and columns of U and V are orthogonal unit vectors. The rows of U are cardiac phases while the columns of U are PCLs of X over space. The rows of V are cardiac segments while the columns of V are PCLs of X over time.

A)



B)

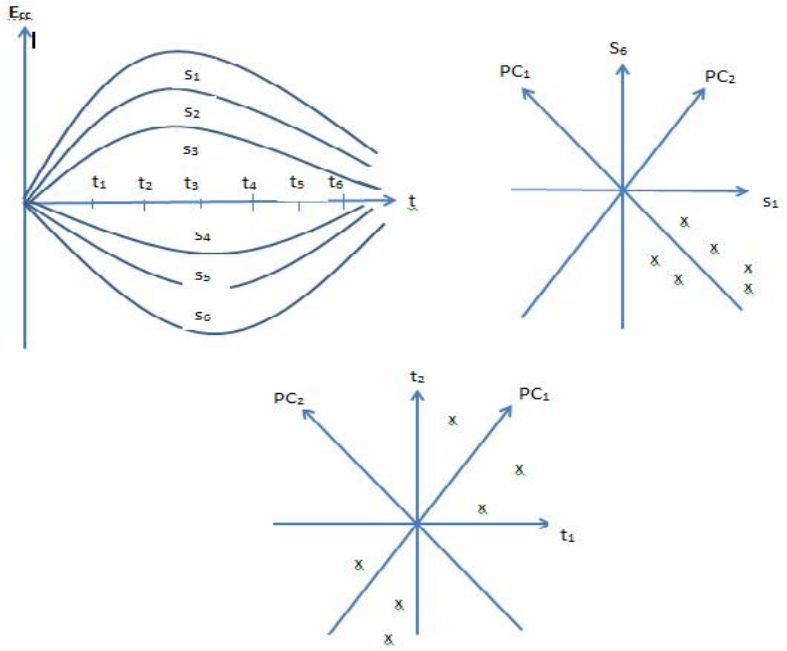


Figure 2-3: Outline of PCA-based quantification of LV dyssynchrony from LV E_{cc}: Expression of LV E_{cc} in the space-time domain, principal component-space domain and principal component-time domain in A) synchronous LV contraction and B) dyssynchronous LV contraction

2.3.a. PCA basis functions over time

Two different approaches towards quantifying regional LV dyssynchrony from MRI-derived LV strains have been developed: 1) PCA-based transform filtering over time; and 2) PCA-based coefficient analysis over space. In the first approach, the PCLs of the matrix U are used to transform X into the principal component-time domain, as seen in Figure 2-3 A. The resulting strain values in the principal component-time domain for each principal component are termed principal component scores (PCSs). The PCSs are calculated using the following linear transformation of X, as shown below:

Equation 2: $$Y = U^T X$$

In order to extract the most significant principal component of the LV strain, the PCS for the 1st (most significant) principal component is transformed back into the space-time domain using the following transformation shown below:

Equation 3: $$X_{tr} = U_1 Y_1$$

In this equation, X_{tr} represents the transformation of the 1st principal component of strains from the principal component-time domain to the space-time domain. Y_1 contains the PCSs for the 1st principal component while U_1 represents the basis function or PCLs for the 1st principal component.

2.3.b. PCA basis functions over space

The extraction of the most significant principal component and transformation back into the space-time domain has the equivalent effect of retaining only the most significant variations in the LV strain and filtering out the higher order principal components. Such filtering enables attenuation of characteristics of the LV strain-time curves that confound their variation over space such as noise and other high frequency variations. In the second approach, PCA over space, the PCLs for the 1st principal component of the matrix V are compared for different LV spatial segments to identify LV regions that are positively or negatively correlated with each other in the principal component-space domain, as seen in Figure 2-3 B.

2.4 Construction of PCA-based LV dyssynchrony parameters

From the methods described above, it is possible to formulate metrics of LV regional dyssynchrony that are based solely on the variations of the raw myocardial strain data over space. These metrics are time-independent and immune to user subjectivity and hence represent a less biased quantification of LV dyssynchrony in comparison to CURE.

In PCA over time, the principal component-time domain is used to filter out all but the most significant principal components, and LV dyssynchrony can be quantified using the coefficient of variation (CV) of X_{tr}, where high values indicate greater dyssynchrony. This metric of LV dyssynchrony has been termed First Order Regional Metric of Estimated Disparity (FORMED) and is calculated as follows:

Equation 4: $$FORMED(t) = \frac{\sigma(X_{tr})}{\sum_{i=1}^{N} |X_{tr}(i,t)|}$$

where σ denotes the standard deviation of X_{tr} over space. While FORMED appears to be a function of time, FORMED(t) is in fact the same for all time points t and hence this metric is time-independent. The time independence of FORMED is due to the fact that the coefficient of variation of X_{tr} is the same over all time points. Since the means of X_{tr} vary substantially for canines with synchronous LV contraction compared to those with LV dyssynchrony, the coefficient of variation provides a normalized measure of dispersion of X_{tr} over space which can be used to identify regional heterogeneity in LV contraction.

In PCA over space, spatial variation in PCLs for the 1st principal component (PCL_1) is examined in the principal component-space domain. LV dyssynchrony can be quantified by the sum of the magnitude of PCL_1 normalized by its L_1 norm (0-dyssynchrony, 1-synchrony). The L_1

norm is simply the sum of the absolute value of PCL_1. This metric of LV dyssynchrony has been termed First Order Regional Conformity Estimate (FORCE) and is calculated as follows:

Equation 5: $$FORCE = \frac{|PCL_1(U)|}{||PCL_1(U)||_1}$$

where$||\ ||_1$ denotes L_1 norm

The metric FORCE accounts for both the signs and magnitudes of the PCL_1 entries [22].

Comparison of FORCE and FORMED with CURE

As shown previously, CURE is defined as the square root of the ratio of the zero order Fourier coefficient of the spatial distribution of strain at a defined time point in the cardiac cycle divided by the sum of the zero and first order coefficients as shown in the equation below:

Equation 6: $$CURE(t) = \sqrt{(\frac{\sum S_0(t)}{\sum(S_0(t)+S_1(t))}}$$

The zero order component (constant term) corresponds to the average magnitude of the strain without frequency modulation, while the first order component corresponds to low spatial frequency variations in strain. In a synchronous heart, the strain is expected to have little regional variation resulting in a high $S_0(t)/S_1(t)$ ratio while a dyssynchronous heart has significant regional strain variation or a low $S_0(t)/S_1(t)$ ratio. This gives a dyssynchrony parameter ranging from 0 to 1, with values closer to 1 indicating greater synchrony This parameter is called CURE for LV E_{cc} but is known as radial uniformity ratio estimate (RURE) for LV E_{rr}.

FORCE, FORMED and CURE/RURE were calculated for all 14 canines (5 LBBB-HF, 5 NQRS-HF and 4 normal) with the aim of comparing the new PCA-based metrics FORCE and FORMED with CURE/RURE, the current measure of LV dyssynchrony from MRI-derived LV strains. Linear correlations between CURE/RURE and the new metrics were calculated to check the agreement of the new metrics with CURE/RURE.

As mentioned earlier, the LBBB-HF canines were models of LV dyssynchrony in heart failure caused by left bundle branch block, the NQRS-HF canines were models of LV synchrony in heart failure and the normal canines were models of LV synchrony in normal animals. Statistical significances between LBBB-HF vs NQRS-HF ($p<0.05$), LBBB-HF vs Normal ($p<0.05$) and NQRS-HF vs Normal ($p>0.05$) were tested using the Mann-Whitney rank sum test. In order to quantify the performance of the metrics, median differences between LBBB-HF vs NQRS-HF and LBBB-HF vs Normal for all three metrics were evaluated using the Hodges-Lehmann non-parametric estimator.

The Mann-Whitney rank is ideal for identifying significance of LV dyssynchrony metrics between pairs of canine groups due to the small sample sizes and unknown probability distributions of each group. The Hodges-Lehmann estimate of median differences calculates the median of all possible pairwise differences between the two groups and is ideal in this case since probability distributions of LV metrics for each group of canines is non-normal as seen from the asymmetry of the median about the 25^{th} and 75^{th} percentiles in box-plots of each of the LV metrics in the following chapter. This analysis was replicated for all the strain quantities and short-axis slices of interest, namely: basal LV E_{cc}, mid-ventricular LV E_{cc}, basal LV E_{rr} and mid-ventricular E_{rr}.

In CRT patient studies described subsequently, LV E_{rr} values were not used for LV dyssynchrony estimation since E_{rr} was not expected to provide accurate measures of dyssynchrony and its sub-optimal performance was verified in the canine studies of LV dyssynchrony mentioned above.

2.5 Quantification of LV dyssynchrony using cine DENSE MRI-based dyssynchrony parameters (clinical CRT trial)

Evaluation of CURE, FORCE, FORMED for selection of heart failure patients for CRT

After validation of FORCE in a canine model of HF, CURE and FORCE were calculated from cine DENSE MR images of the LV in a clinical trial of 70 heart failure patients referred for CRT. The aim of this preliminary clinical study was to design a better method for appropriate selection of CRT patients using CURE.

A subset of these CRT patients that had the best chance of benefiting from CRT was chosen using the following physiological criteria [23]:

i) absence of scar as determined from late gadolinium- enhanced (LGE) MRI (% of LV scar volume<10%)

ii) LV lead delay time with respect to QRS segment (QLV) /QRS width>=50%, i.e. abnormal electrical timing at LV lead site

The above criteria of absence of scar and irregular electrical timing at LV lead site were favorable conditions for optimal CRT outcome and 23 out of 70 patients met these criteria. The

calculation of LV E_{cc} was performed in largely the same way as for the canines except that strains were calculated only for systole and the first few frames of diastole (typically about 60% of the acquired time frames). The reason for computing only systolic strains was that the patient studies aimed at establishing metrics of LV dyssynchrony that could select patients with systolic heart failure for whom CRT would be beneficial, i.e. systolic regional dyssynchrony was explored in these patients.

Imaging methods to quantify LV dyssynchrony for CRT patient selection

Imaging parameters for the cine DENSE sequence for all the CRT patients included field of view = 340 – 400 mm^2, matrix = 128 × 128, slice thickness = 8 mm, flip angle = 20°, TR = 17 ms, TE = 1 ms, number of spiral interleaves = 6, fat suppression, temporal resolution = 17 ms, and displacement encoding frequency = 0.1 cycles/mm [24].

Analysis of performance of CURE, FORCE and FORMED in identifying CRT candidates

After obtaining LV E_{cc} from each short-axis cine DENSE slice (base, mid-base, mid, mid-apex), CURE and FORCE were calculated for each slice. The final CURE, FORCE and FORMED values for each patient were then calculated by the following procedure:

If the CURE or FORCE values for the base, mid-base, mid and mid-apex slices are x_1, x_2, x_3, and x_4 respectively, then

$y_1=\min(x_1,x_2)$

$y_2=\text{mean}(x_1,x_2,x_3,x_4)$

$y_{final}=\min(y_1,y_2)$

The reason for this method of calculating a final CURE or FORCE value from all short-axis 2D slices of the LV is that higher importance is given to the basal and mid-basal slices but contributions from the mid and mid-apical slices are not excluded if there is extreme dyssynchrony in either of these slices.

LV end-systolic volume (ESV), end-diastolic volume (EDV) and ejection fraction (EF) were calculated from MR images for each of the CRT patients. ESV and EDV indices were calculated by dividing the respective volumes by the body mass index (BMI).

The ESV index was observed before and after CRT and a 15% decrease in ESV index was deemed to represent a positive response to CRT. Consequently, the thresholds for the CURE, FORCE and FORMED values were designed in such a way as to optimize sensitivity and specificity of the LV dyssynchrony measures in identifying positive and negative responses. Finally, the area under the Receiver Operating Characteristics (ROC) curve, i.e. Sensitivity vs (1-Specificity), was calculated for each of the metrics CURE, FORCE and FORMED to determine the ability of each metric to predict CRT patient outcome [25]. Statistical tests were performed to determine whether each metric was able to predict CRT patient outcomes with a probability greater than that expected by chance [26].

An additional analysis was performed on the patient data by calculating functional cardiac parameters and LV dyssynchrony metrics (FORCE, CURE, FORMED) separately for the patients with positive and negative CRT response. The purpose of this additional analysis was to observe statistically significant differences in values of the functional cardiac parameters and LV dyssynchrony metrics between CRT responders and non-responders.

All patient parameters are shown as median, interquartile range (25^{th} percentile, 75^{th} percentile) since sample sizes are too small for the data to be normally distributed.

CHAPTER 3-RESULTS

3.1 Metrics of LV dyssynchrony in canine model of heart failure

Animal Model

Left bundle branch ablation was completed successfully in all LBBB-HF animals as evidenced from the wide QRS duration (~120 ms) and LBBB morphology in these canines; in contrast, QRS duration was 55-60 ms in the NQRS-HF and normal groups. Five weeks of tachy-pacing resulted in LV dysfunction with LV ejection fraction (LVEF) <0.30 in both LBBB-HF and NQRS-HF animals. While LVEF was not significantly different for LBBB-HF vs NQRS-HF, LV end-diastolic volume was significantly larger for LBBB-HF vs NQRS-HF groups (median=110 vs 77 ml, p=0.008). Finally, normal animals had a significantly greater LVEF than HF animals (median=0.57 vs 0.15, p=0.017).

Quantification of Regional LV Dyssynchrony By PCA Over Time

One of the purposes of applying PCA on LV strain data over space and time is to reduce the dimensionality of the data, which can be done by considering only the most significant principal components. From Figures 3-1 A, B and C, it can be clearly seen that the 1st singular value dominates all the other singular values. Since the singular values represent the contributions of each principal component to the variations in the data along a fixed dimension, it is adequate to quantify LV dyssynchrony using only this most significant principal component.

Figures 3-1 A, B and C show the singular values in the singular value decompositions of these strains. In both cases, the first singular value is >50% of the sum of all singular values, implying that the first singular value and by extension the first principal component represents most of the important features of the strain data.

Figures 3-2 A, B and C shows typical circumferential strain results for NQRS-HF and LBBB-HF animals respectively. The figures show the average LV E_{cc} calculated from the 24-segment LV model over every four consecutive segments starting from the anterior sector. This averaging produces average E_{cc} for the standard LV sectors, namely anterior, anterolateral, inferolateral, inferior, inferoseptal and anteroseptal. In the case of NQRS-HF (LV synchrony), the strain curves are fairly uniform over the segments, while in the case of LBBB-HF (LV dyssynchrony) the strain curves show evidence of simultaneous stretch and contraction (i.e., intraventricular LV dyssynchrony).

Using the first basis function in the principal component domain, the strains are then transformed back into the space-time domain, as shown in figures 3-3 A, B and C. These "filtered" strain curves reflect the primary data contained in the first principal component (first order approximation). Also, the "filtered" strains vary smoothly over time. This is possibly because variations over time in regional strains due to motion or other artifacts that corrupt the signal-to-noise ratio of the phase images are stored in higher order principal components.

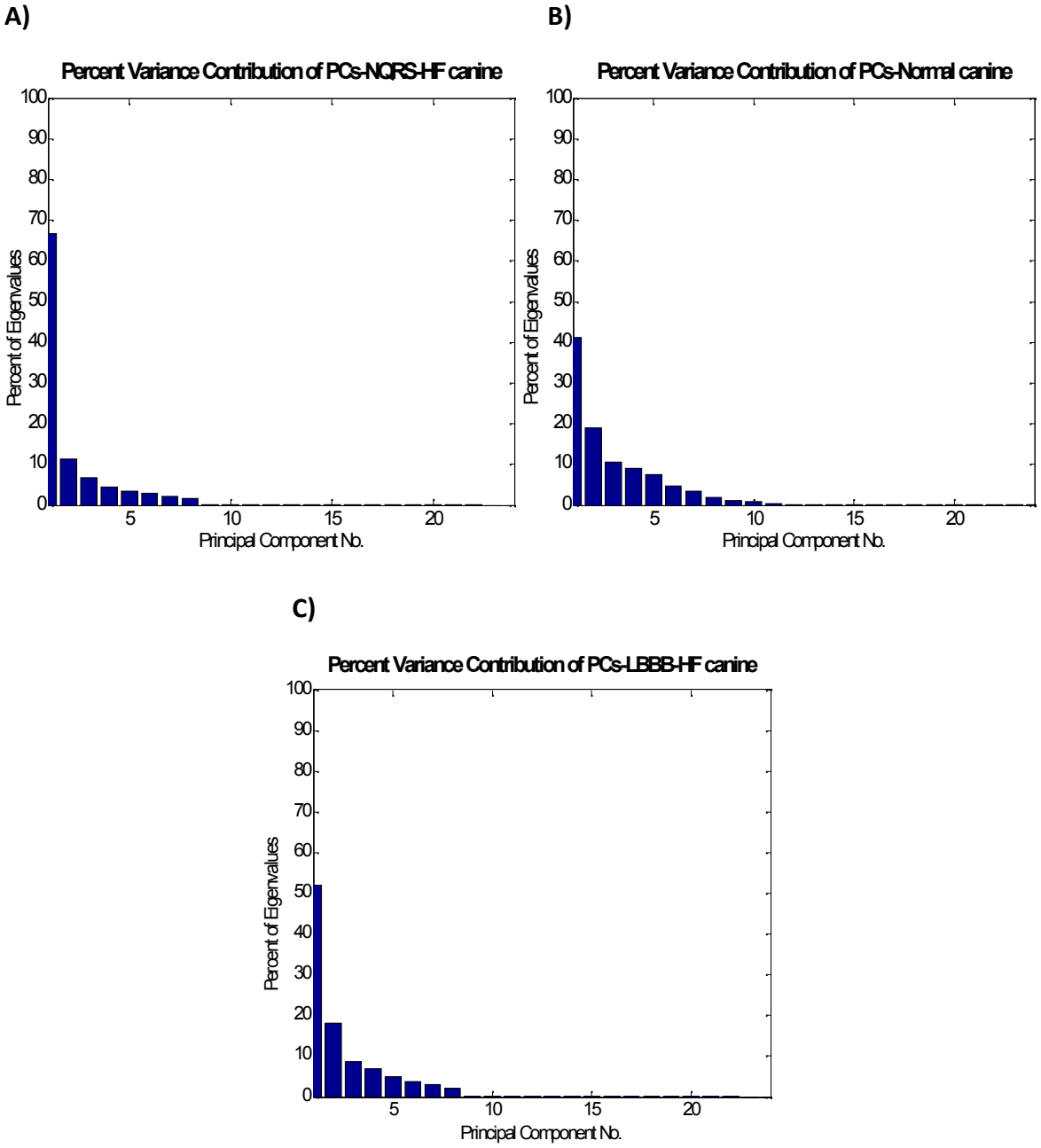


Figure 3-1: Singular values representing relative contributions of principal components to total variance of mid-ventricular LV E_{cc} over space and time for sample A) NQRS-HF, B) Normal and C) LBBB-HF canines.

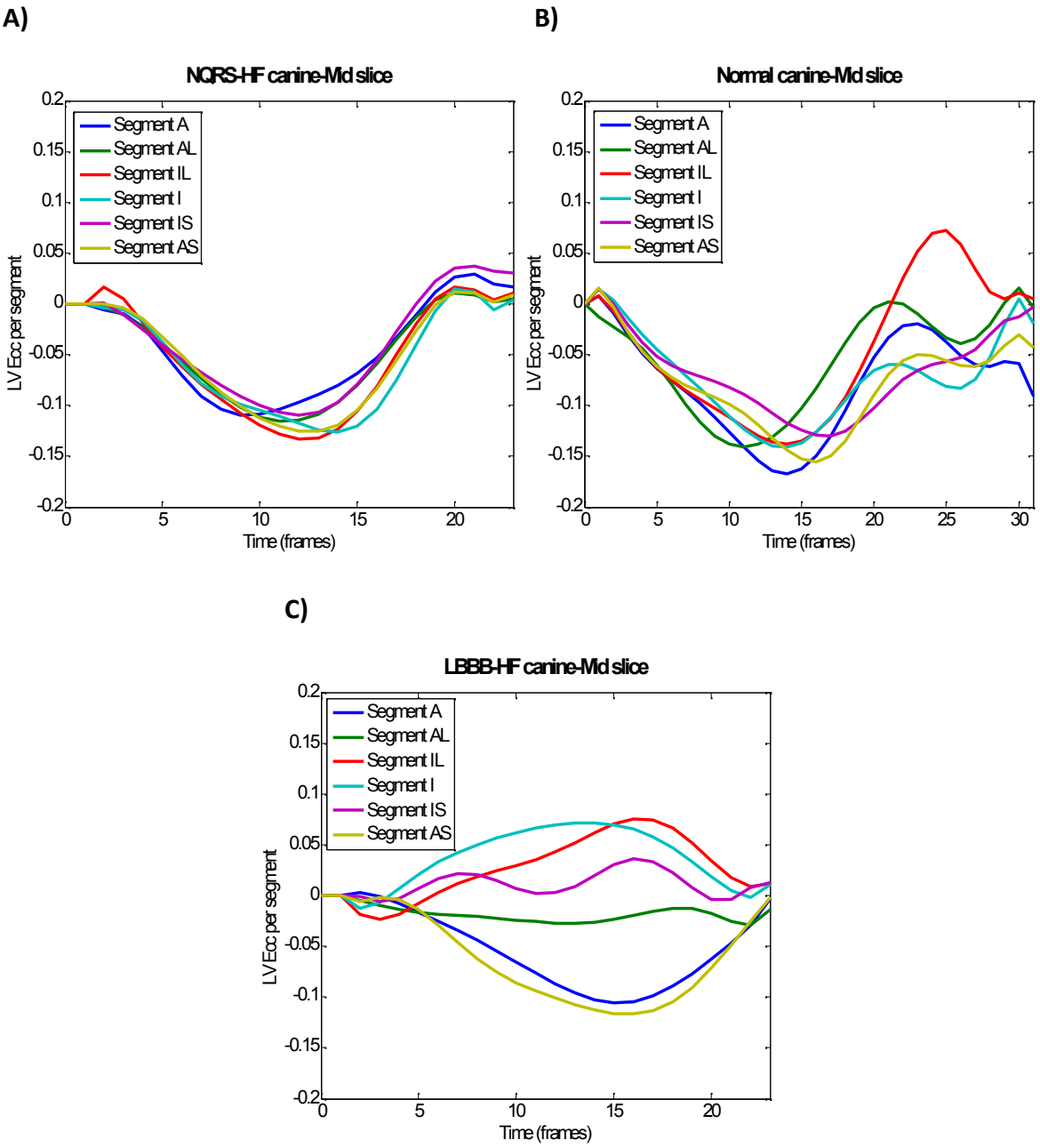


Figure 3-2: Regional mid-ventricular LV E_{cc} over time (cardiac phases) for sample A) NQRS-HF, B) Normal and C) LBBB-HF canines. A-anterior, L-Lateral or antero-lateral, P-posterior or infero-lateral, I-inferior, IS-infero-septal, AS-antero-septal

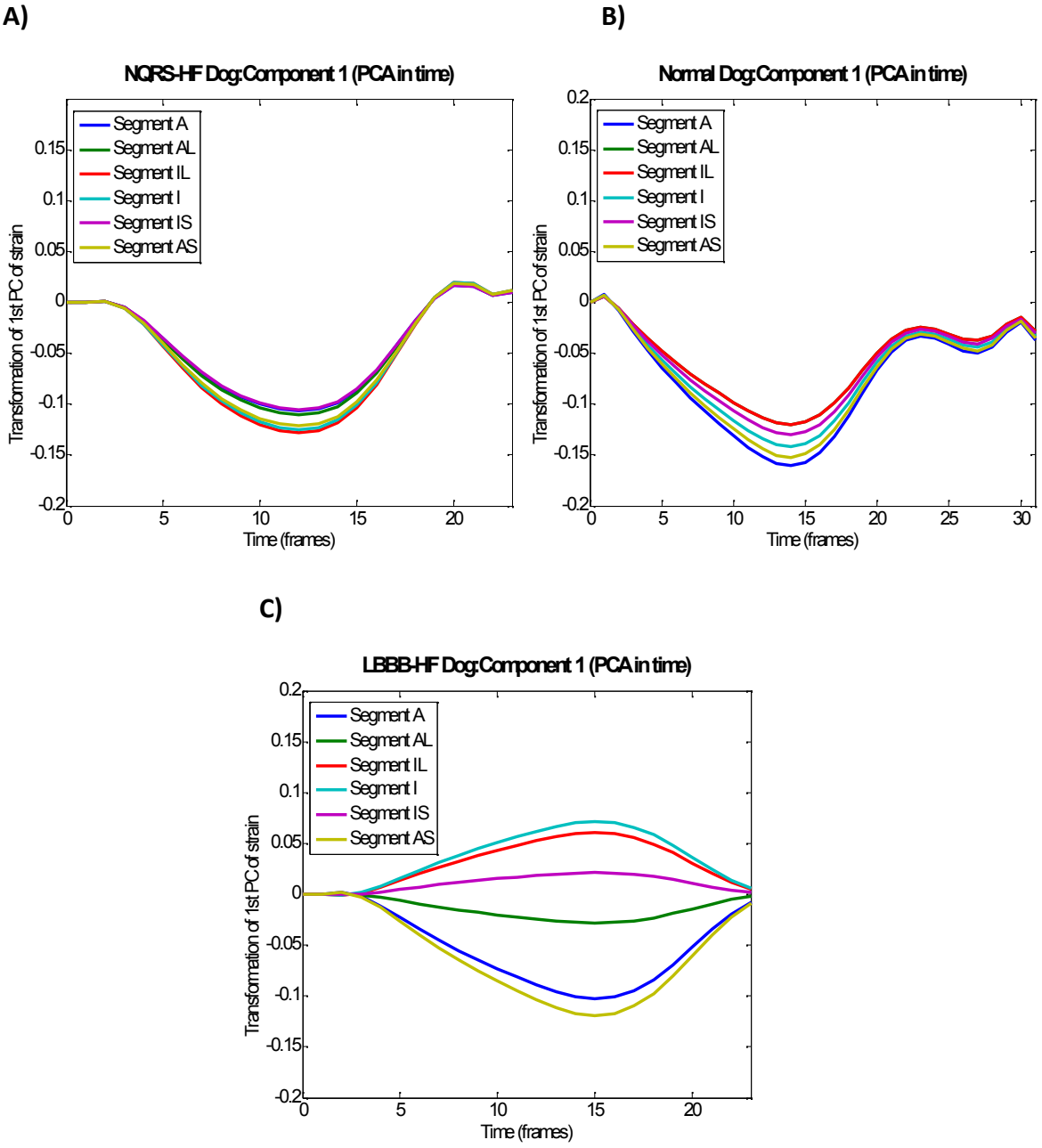
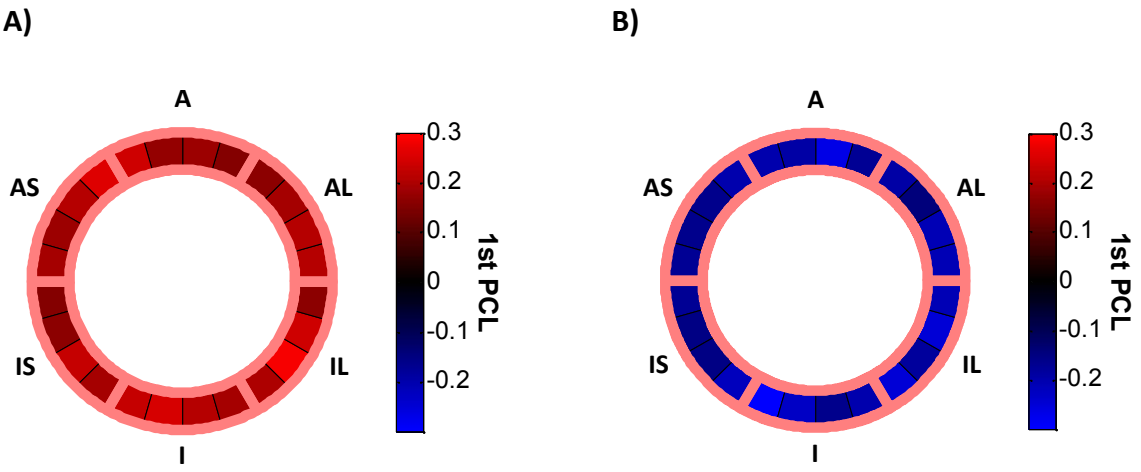


Figure 3-3: Filtered mid-ventricular LV E_{cc} as a function of cardiac phases using 1st principal component basis functions over time (cardiac phases) for sample A) NQRS-HF, B) Normal and C) LBBB-HF canines. A-anterior, AL-lateral or antero-lateral, IL-posterior or infero-lateral, I-inferior, IS-infero-septal, AS-antero-septal

Quantification of Regional LV Dyssynchrony By PCA Over Space

In addition to the analysis based on the first principal component of E_{cc} in time, a separate analysis was simultaneously performed based on the first principal component of E_{cc} in space. Bullseye plots of PCLs for each LV segment are shown in Figures 3-4 A, B and C for representative NQRS-HF, normal and LBBB-HF canines respectively. In this analysis, PCLs of the same sign and similar magnitudes in different LV segments imply uniformity in strain values over segments, i.e all segments contract and relax simultaneously to the same extent, and hence synchronous LV contraction (Figure 3-4 A-B; NQRS-HF, Normal). In contrast, negative PCLs in some segments and positive PCLs in others imply heterogeneity in strain values over segments, i.e. dyssynchronous LV contraction (Figure 3-4 C; LBBB-HF). As expected from a physiologic standpoint, the contrasting negative versus positive PCLs in LBBB-HF canines are segregated in the septal segments versus the posterolateral segments, corresponding to the different mechanical activities (stretch v. contraction) in these segments.



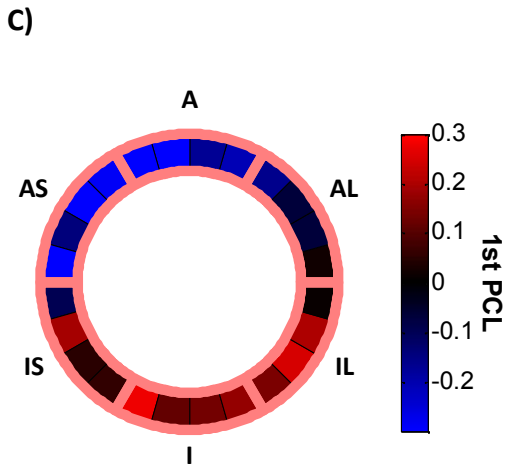


Figure 3-4: Bulls-eye plots of 1st Principal component loadings (PCLs) of LV E_{cc} as a function of space for sample A) NQRS-HF, B) Normal and C) LBBB-HF canines

Using this methodology, parameters based on either PCA in time (FORMED) or PCA in space (FORCE) were calculated as described in Chapter 2, to effectively distinguish LV dyssynchrony associated with LBBB versus LV synchrony associated with a narrow QRS in heart failure. As shown in Figures 3-5 and 3-6 A, B and C, FORCE, FORMED and CURE all provide effective discrimination for LBBB-HF vs NQRS-HF and LBBB-HF vs Normal ($p < 0.05$) for mid-ventricular and basal LV E_{cc} respectively. However, for mid-ventricular and basal LV E_{rr}, RURE and FORMED provide effective discrimination only for LBBB-HF vs Normal ($p < 0.05$). Also, FORCE provides effective discrimination for LBBB-HF vs NQRS-HF and LBBB-HF vs Normal ($p < 0.05$) for basal LV E_{rr} but is not significantly different for any pair of animals for mid-ventricular LV E_{rr} as seen in Figures 3-7 and 3-8 A, B and C. Thus, calculation of LV circumferential dyssynchrony metrics using LV E_{cc} is better for distinguishing LV synchrony from LV dyssynchrony than LV radial dyssynchrony metrics calculated using LV E_{rr}.

For normal controls and NQRS-HF canines, the interquartile range for FORCE was significantly less than that for CURE/RURE. For both of these tests, FORCE provided a tighter distribution with less variance for NQRS and normal cases than FORMED. Since an ideal metric of LV dyssynchrony should have little inter-individual variance for synchronous LV contraction, our preliminary studies in a canine model of HF suggest that FORCE is the more optimal metric of LV dyssynchrony.

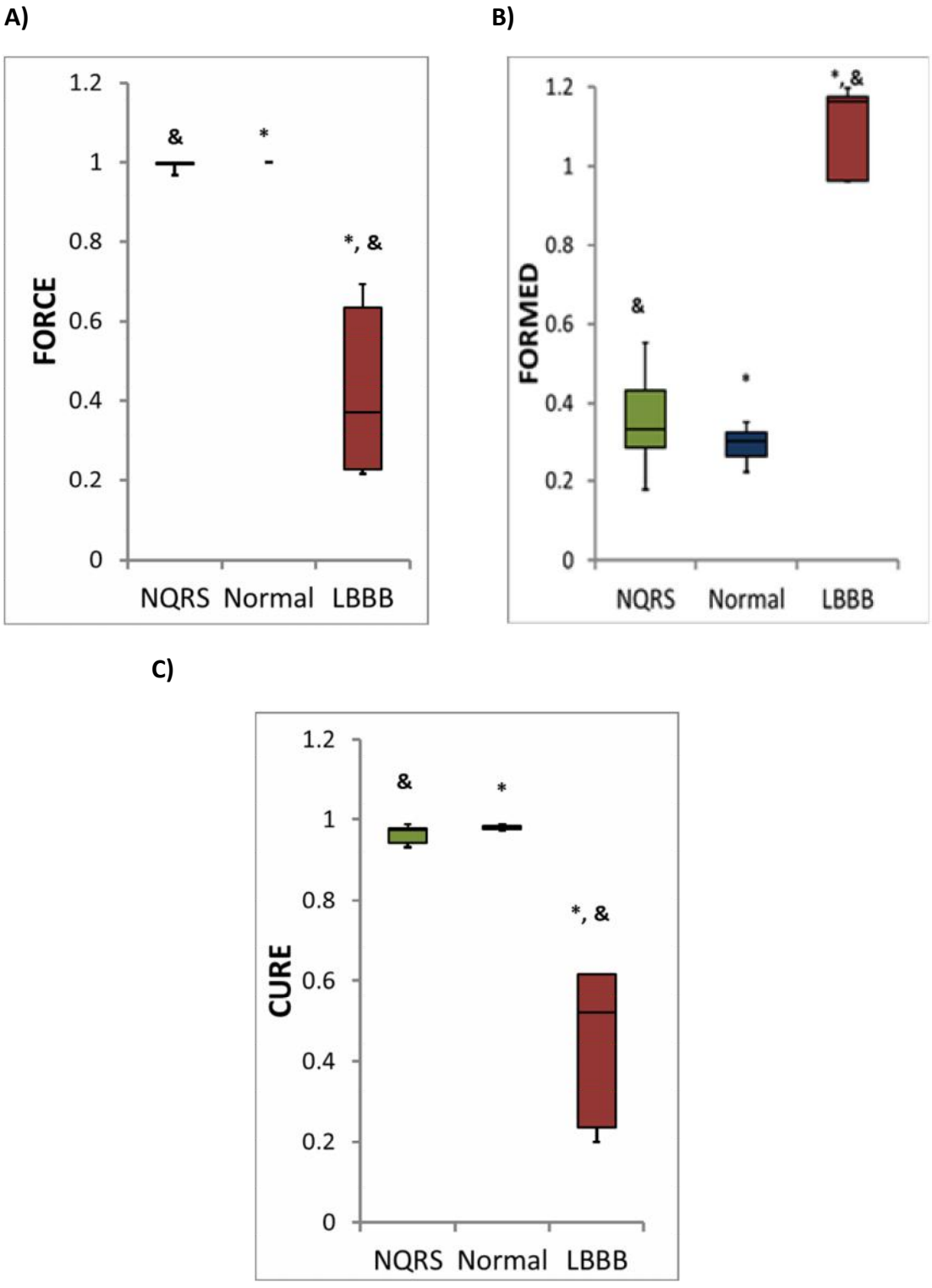


Figure 3-5: Box plots of LV dyssynchrony metrics: A) FORCE, B) FORMED and C) CURE for LV mid-ventricular Ecc in LBBB-HF, NQRS-HF and normal canines; *-$p<0.05$ for LBBB-HF vs Normal, &-$p<0.05$ for LBBB-HF vs NQRS-HF

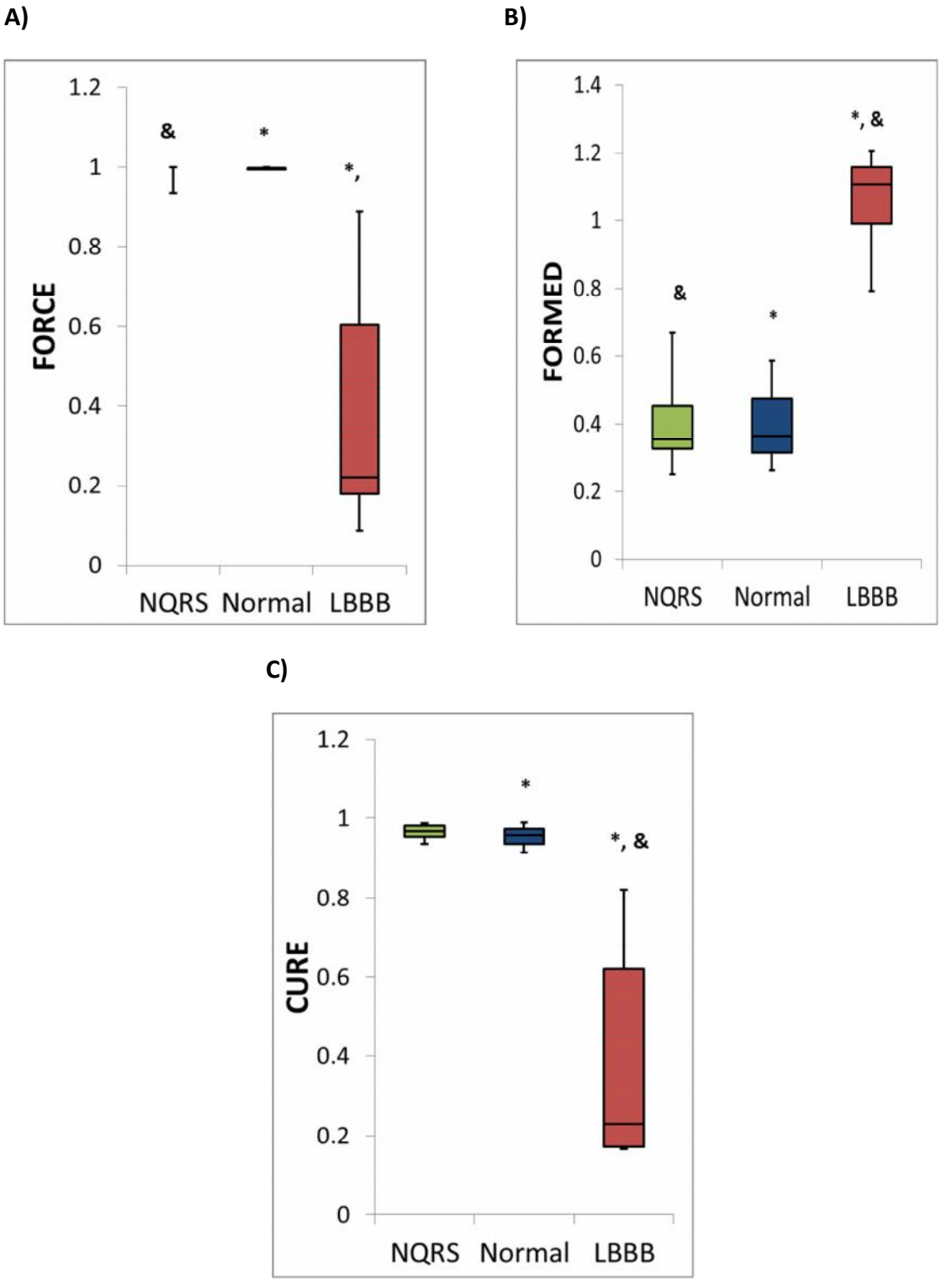


Figure 3-6: Box plots of LV dyssynchrony metrics: A) FORCE, B) FORMED and C) CURE for LV basal Ecc in LBBB-HF, NQRS-HF and normal canines; *-p<0.05 for LBBB-HF vs Normal, &-p<0.05 for LBBB-HF vs NQRS-HF

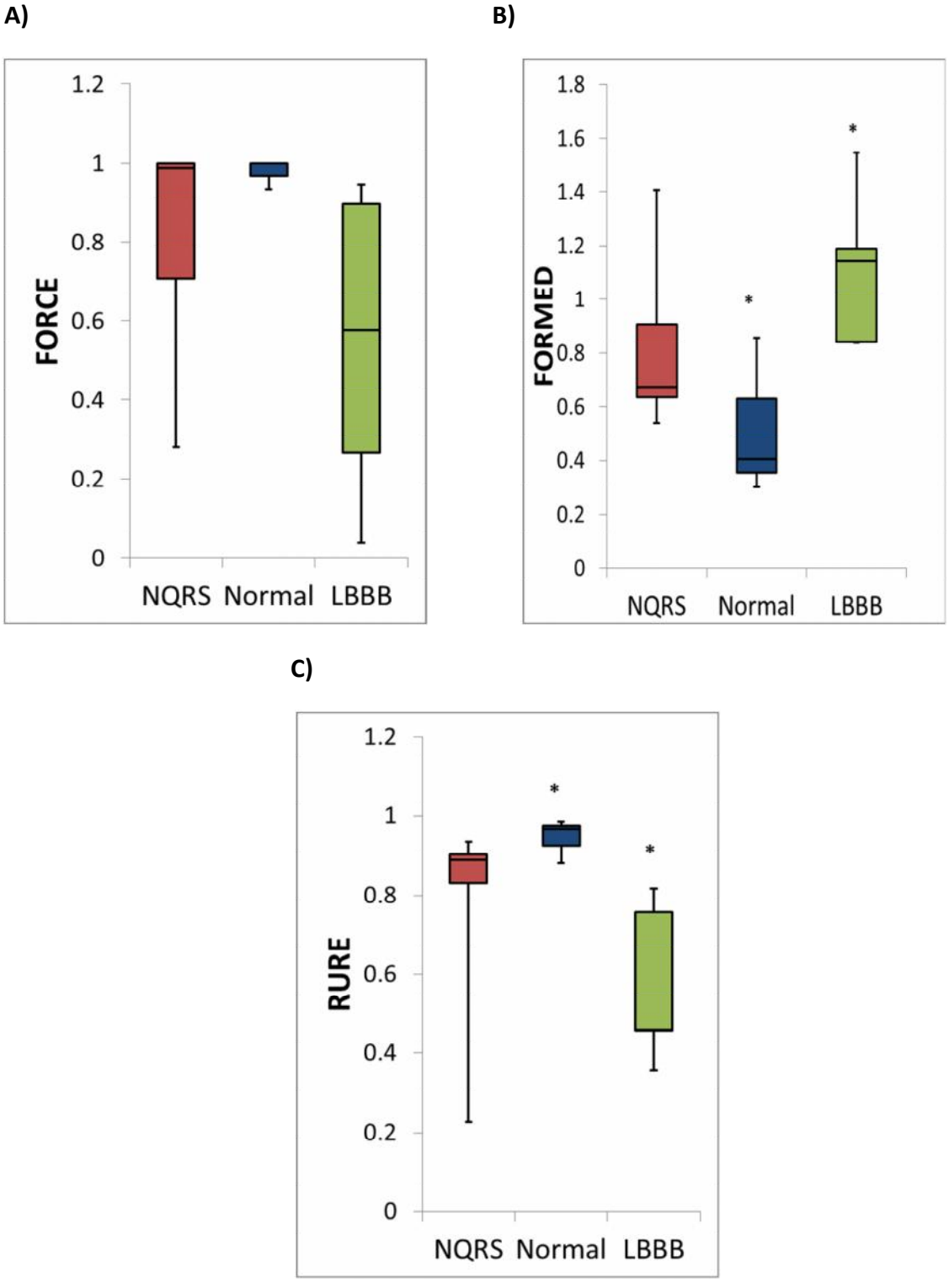


Figure 3-7: Box plots of LV dyssynchrony metrics: A) FORCE, B) FORMED and C) RURE for LV mid-ventricular Err in LBBB-HF, NQRS-HF and normal canines; *-p<0.05 for LBBB-HF vs Normal

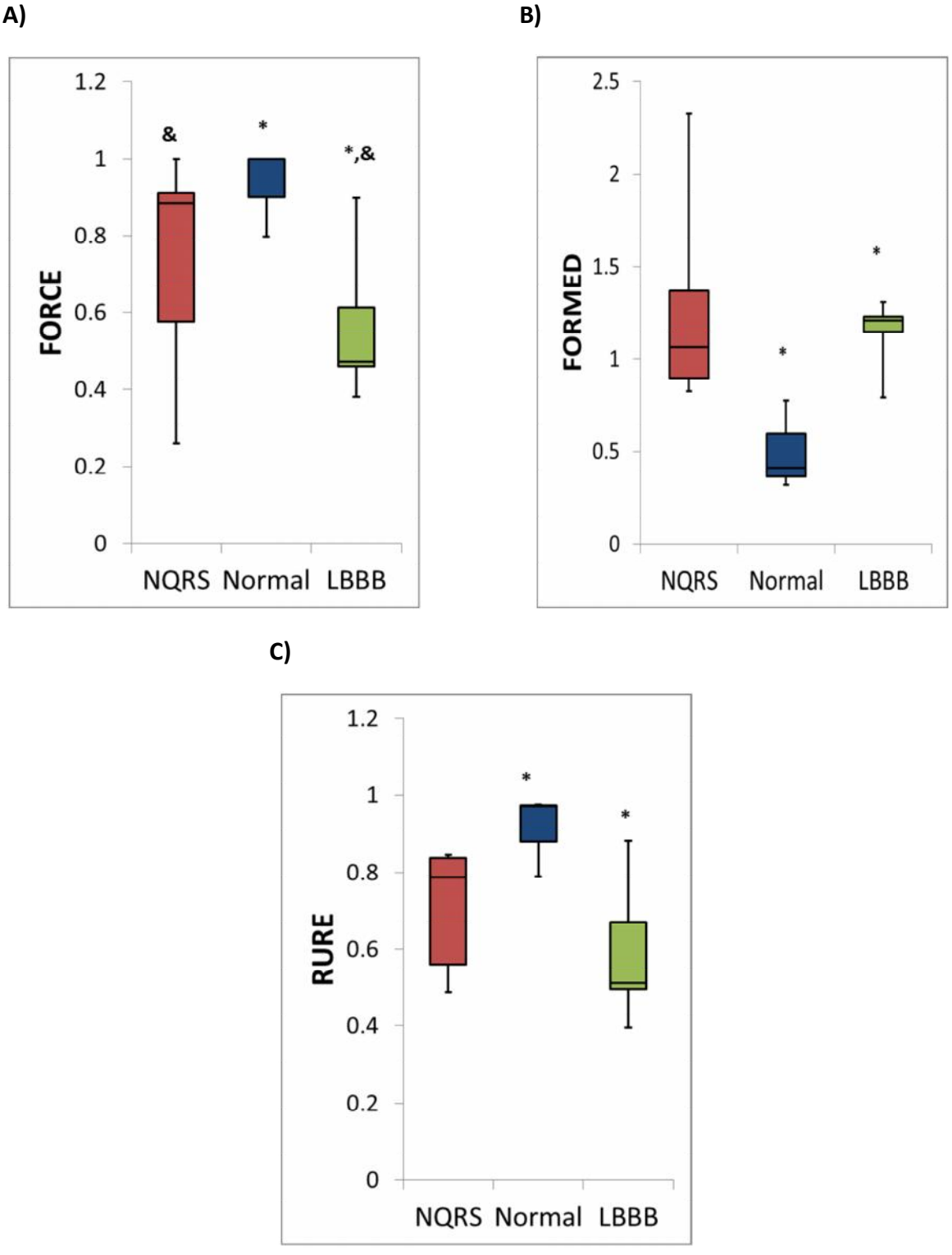


Figure 3-8: Box plots of LV dyssynchrony metrics: A) FORCE, B) FORMED and C) RURE for LV basal Err in LBBB-HF, NQRS-HF and normal canines; *-p<0.05 for LBBB-HF vs Normal, &-p<0.05 for LBBB-HF vs NQRS-HF

3.2 Metrics of LV dyssynchrony in HF patients as criteria for CRT patient selection

CURE, FORCE and FORMED values were calculated from all available cine DENSE MRI short-axis slices as per the procedure outlined in the previous chapter. Functional cardiac parameters for a subset of CRT patients are shown in Table 3-1:

23 patients w/ no scar and QLV/QRS width>=50%	Median, interquartile range (IQR)
Age	64.0, (59.1 to 71.7)
Gender	52.2% female
% LVEF	25.6, (19.7 to 29.4)
LVESV index (cc/m^2)	87.9, (71.7 to 122.3)
% change in LVESV index post-CRT	-22.1, (-46.9 to -3.2)
% CRT responders (>=15% decrease in LVESV index post-CRT)	69.6

Table 3-1: Patient parameters for identification of LV dyssynchrony in the context of CRT in a subset of CRT patients (n=23) using baseline cine DENSE MRI

This subset of 23 CRT patients is indicative of a population with severely impaired LV contraction and can thus be benefited by CRT as shown by a response rate of nearly 70%.

The ability of each of the metrics to predict CRT outcomes is shown in Table 3-2:

	Sensitivity	Specificity
CURE (cutoff=0.7)	1	0.714
FORCE (cutoff=0.795)	1	0.714
FORMED (cutoff=0.9)	1	0.429

Table 3-2: Sensitivity and Specificity of LV dyssynchrony metrics CURE, FORCE and FORMED in identifying positive CRT response in a subset of CRT patients (n=23) using baseline cine DENSE MRI

The cutoffs above were chosen in such a way as to optimize the specificity of each LV dyssynchrony metric and attain 100% sensitivity, i.e. all patients with positive CRT outcome are identified correctly. The cutoffs for CURE and FORCE are values below which a patient is assumed to have LV dyssynchrony while the cutoff for FORMED is the value above which a patient has LV dyssynchrony.

Sensitivity is the rate of true positives which in this context is the proportion of patients with decrease in LVESV index post-CRT>=15%, i.e. positive clinical response, that have CURE<0.7 or FORCE<0.795 or FORMED>0.9, i.e. LV dyssynchrony. Similarly, specificity is the rate of true negatives or in this case, the proportion of patients with increase in LVESV index or decrease in LVESV index post-CRT<15%, i.e. negative clinical response, that have CURE>=0.7 or FORCE>=0.795 or FORMED<=0.9.

As we can see above, FORCE and CURE have the highest specificity of the three metrics indicating their suitability in selection of CRT patients while FORMED has the worst specificity. The thresholds were adjusted for 100% sensitivity while sacrificing specificity since it is important that all patients that would benefit from CRT receive therapy to reduce the

probability of heart failure hospitalizations and subsequent death. However, if some patients that do not benefit from CRT receive therapy, i.e. <100% specificity, it is not life-threatening and is mostly just a waste of money and resources.

Finally, patient parameters and LV dyssynchrony metrics were evaluated separately for CRT-responders and CRT non-responders as shown in Table 3-3:

	CRT-responders (16) Mean +/- std. deviation	CRT-non-responders (7) Mean +/- std. deviation
Age (years)-Median, IQR	63.5, (57.6 to 71.4)	69.9 , (61.3 to 72.0)
Gender	68.8% female	14.3 % female
% LVEF	23.8 +/- 7.8	24.2 +/- 9.5
LVESV index (cc/m^2)	91 +/- 40.3	110.8 +/- 29
% change in LVESV index post-CRT	-39.5 +/- 18	13.7 +/- 20.8 *
CURE	0.395 +/- 0.208	0.689 +/- 0.268 *
FORCE	0.365 +/- 0.239	0.735 +/- 0.333 *
FORMED	1.091 +/- 0.104	0.906 +/- 0.204 *

Table 3-3: Comparison of functional cardiac parameters and LV dyssynchrony metrics for CRT responders and non-responders; * p-value<0.05-Equal Variance Test

As expected, % decrease in LVESV index post-CRT was higher with higher FORMED and lower CURE and FORCE values for CRT responders compared to CRT non-responders. Also, while LVESV index and LVEDV index were lower for CRT responders, EF was similar for both groups indicating similar cardiac pumping capacities for both groups. Curiously, a higher

proportion of CRT responders were female compared to the same proportion for CRT non-responders suggesting that female HF patients tend to have better CRT outcomes.

CHAPTER 4-DISCUSSIONS AND CONCLUSIONS

4.1 Discussions

4.1.a. PCA-based measures of LV dyssynchrony in canines

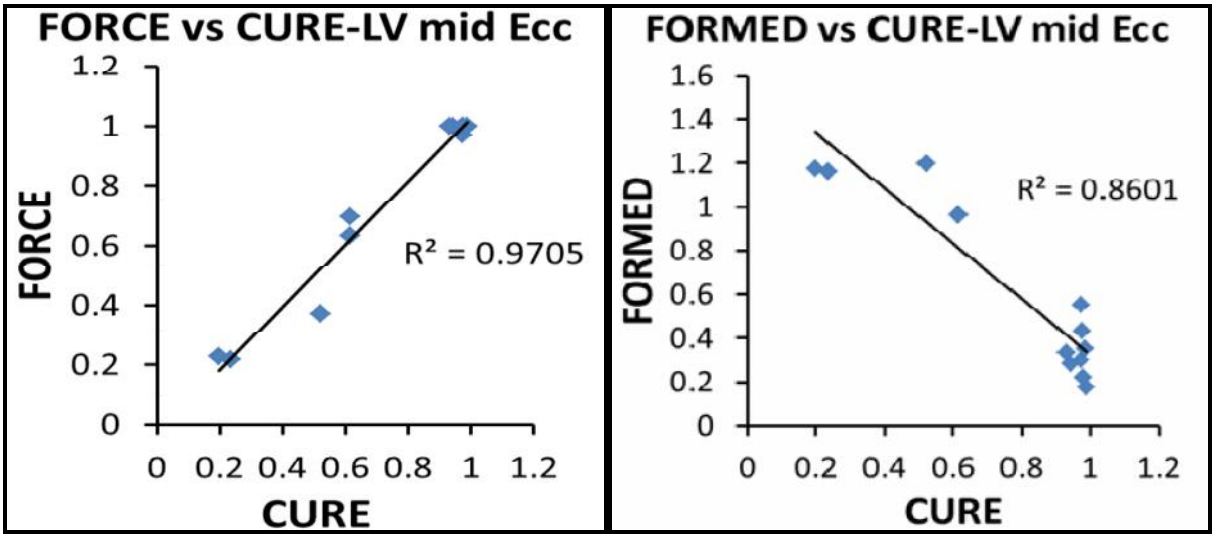
Key Findings

The key findings of this analysis are that using PCA to quantify mechanical dyssynchrony based on cine DENSE MRI data is feasible and accurately identifies prototypical mechanical dyssynchrony resulting from LBBB in heart failure. The PCA-based methods automatically generate a single time-independent parameter that comprehensively characterizes spatial mechanical dyssynchrony from all regional strains over the entire cardiac cycle. Also, accurate characterization of inefficient cardiac contraction patterns due to non-uniformity can be accomplished with PCA without the need for fitting the data to a pre-specified mathematical function, resulting in a completely data-driven result. In addition, both PCA in space and PCA in time approaches effectively identify mechanical dyssynchrony and provide complementary assessments that are being further evaluated in the clinical assessment of HF patients referred for CRT. Finally, The PCA parameter FORCE and the FT-based parameter CURE are strongly linearly correlated with each other (R^2=0.97). The alternative PCA parameter FORMED is also strongly linearly correlated to CURE (R^2=0.86) as seen in Figure 4-1 A for mid-ventricular LV E_{cc}.

For basal LV E_{cc}, FORCE and FORMED are also strongly correlated to CURE (R^2=0.99 and 0.85 respectively) as seen in Figure 4-1 B. Similarly, for mid-ventricular LV E_{rr}, FORCE and FORMED are strongly correlated to RURE (R^2=0.82 and 0.81 respectively) while FORCE is

strongly correlated to RURE for basal LV E_{rr} (R^2=0.85) as seen in Figures 4-2 A and B. Only FORMED for basal LV E_{rr} has a slightly weaker correlation with RURE (R^2=0.60) as seen in Figure 4-2 B.

A)



B)

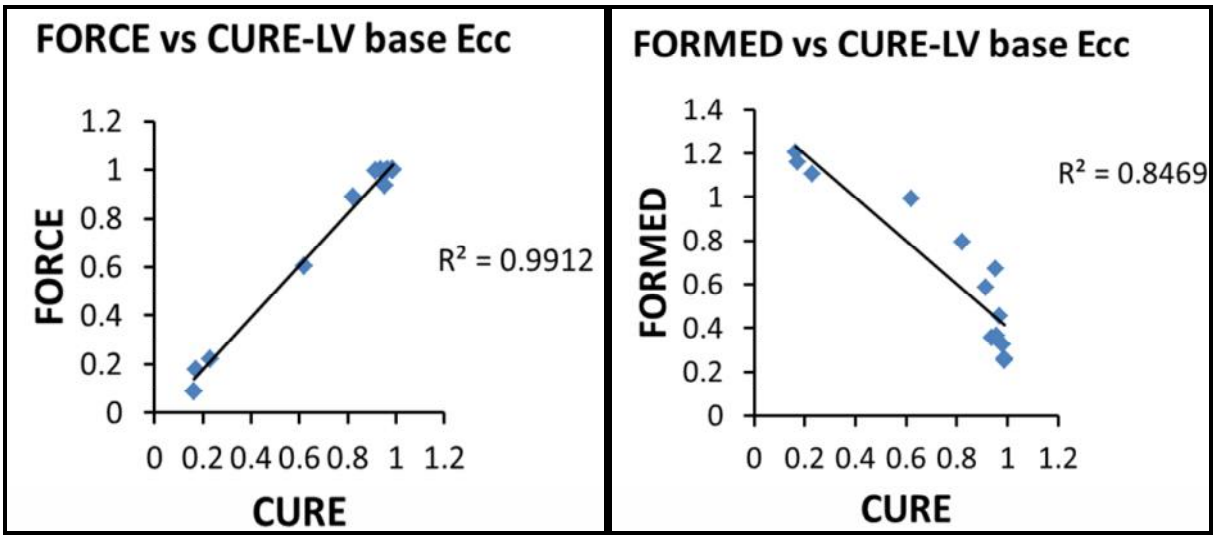
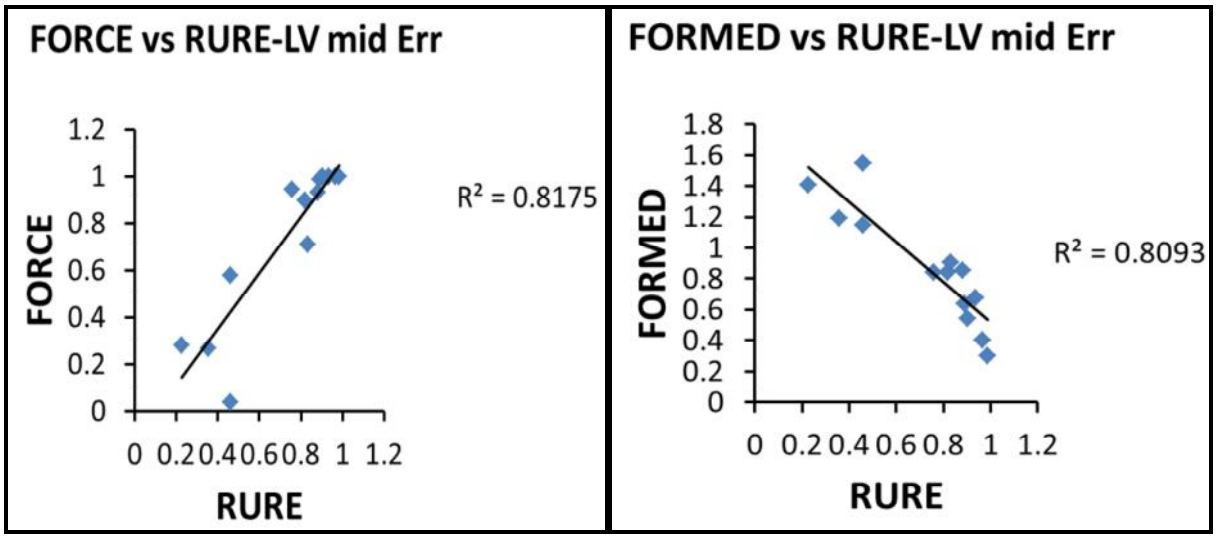


Figure 4-1: Linear correlation plots of FORCE, FORMED vs CURE for A) mid-ventricular LV E_{cc} and B) basal LV E_{cc}

A)



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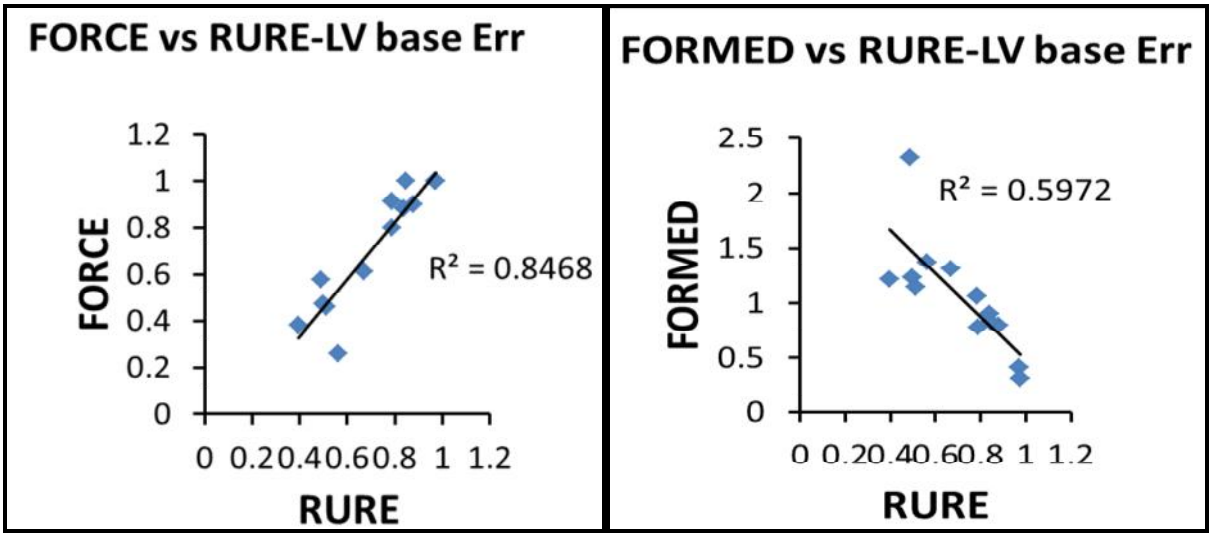


Figure 4-2: Linear correlation plots of FORCE, FORMED vs RURE for A) mid-ventricular LV E_{rr} and B) basal LV E_{rr}

The above results indicate that for all groups of canines, there is a strong linear relationship between the three LV dyssynchrony metrics under study, namely FORCE, FORMED and CURE/RURE.

Comparison with FT-based analysis

FT analysis of regional circumferential strain based on CURE has a high predictive accuracy for identifying patients with improvement in function class after CRT [10]. Furthermore, FT-based CURE identifies mechanical dyssynchrony more effectively than analysis of differences in time to peak strain [12]. As previously described, this FT-based method determines dyssynchrony based on the ratio of the zero order term and the sum of the zero and first order terms of the function of strain versus regional segment. This parameter with range 0-1 (0=dyssynchrony; 1=synchrony) characterizes mechanical dyssynchrony at a fixed time point; therefore, in order to characterized mechanical dyssynchrony over the entire cardiac cycle, it is necessary to average the CURE for time points in systole and early diastole.

In contrast, the PCA methodology integrates mechanical dyssynchrony for all LV segments throughout the cardiac cycle without the need for time averaging or selection of certain time points. In addition, the FT method is based on the assumption that the strain versus segment function can be fit to a sine/cosine function in order to determine the contributions of lower and higher frequency components. PCA makes no such assumption and is completely "data-driven" in this sense.

The correlation between PCA and FT-based analyses is reassuring, and the fact that PCA-based methods distinguish mechanical dyssynchrony from synchrony at least as well as CURE is also noteworthy. As shown in Table 4-1, the median differences in FORCE and FORMED for LBBB-HF vs NQRS-HF and LBBB-HF vs Normal along with associated confidence intervals for mid-ventricular and basal LV E_{cc} indicate a high level of discrimination that is at least as good as

what is obtained for CURE. Also, all three metrics show very small differences for NQRS-HF vs Normal indicating successful identification of synchrony for mid-ventricular and basal LV $E_{cc.}$

On the other hand, the median differences for LBBB-HF vs Normal tend to be pretty large compared to those for LBBB-HF vs NQRS-HF and NQRS-HF vs Normal for both FORCE and RURE for mid-ventricular and basal LV E_{rr} as shown in Table 4-2. These observations and the lengths of the confidence intervals indicates that these metrics are inconsistent in identifying dyssynchrony from mid-ventricular and basal LV E_{rr}. For FORMED applied on mid-ventricular and basal LV E_{rr}, the large differences between NQRS-HF vs Normal indicate a tendency of this metric to identify spurious abnormalities contraction and relaxation in radial strains in NQRS-HF animals.

Based on the box plots in Chapter 3 displaying the metrics FORCE, FORMED and CURE/RURE for each category of canine, the correlation plots shown previously in this chapter and the table of differences in metrics between groups of canines shown below, circumferential strain is more suitable for quantification of LV dyssynchrony since it distinguishes between canines with LV dyssynchrony (LBBB-HF) and those with LV synchrony (NQRS-HF and Normal) effectively. Since the metrics work well for mid and base LV E_{cc}, a combination of LV E_{cc} from short-axis slices was used for quantifying LV dyssynchrony in the clinical CRT studies.

		Median difference (95% confidence interval)		
Mechanical parameter	Dyssynchrony metric	LBBB-HF vs NQRS-HF	NQRS-HF vs Normal	LBBB-HF vs Normal
LV mid Ecc	FORCE	-0.629 (-0.779 to -0.306)	0 (-0.031 to 0)	-0.629 (-0.783 to -0.306)
	FORMED	0.742 (0.531 to 0.914)	0.061 (-0.175 to 0.330)	0.822 (0.609 to 0.975)
	CURE	-0.452 (-0.754 to -0.328)	-0.010 (-0.056 to 0.016)	-0.458 (-0.789 to -0.357)
LV base Ecc	FORCE	-0.780 (-0.911 to -0.113)	-0.004 (-0.064 to 0.006)	-0.776 (-0.911 to -0.107)
	FORMED	0.668 (0.436 to 0.856)	-0.010 (-0.334 to 0.409)	0.628 (0.207 to 0.945) -
	CURE	-0.737 (-0.809 to -0.160)	-0.009 (-0.073 to 0.053)	-0.728 (-0.824 to -0.093)

Table 4-1: Hodges-Lehmann estimates of median differences and 95% confidence intervals between different groups of canines for the three metrics of LV dyssynchrony: CURE, FORCE and FORMED for LV Ecc in mid-ventricular and basal slices.

		Median difference (95% confidence interval)		
Mechanical parameter	Dyssynchrony metric	LBBB-HF vs NQRS-HF	NQRS-HF vs Normal	LBBB-HF vs Normal
LV mid Err	FORCE	-0.131 (-0.735 to 0.237)	-0.013 (-0.721 to 0.67)	-0.423 (-0.962 to 0.012)
	FORMED	0.282 (-0.220 to 0.648)	0.269 (-0.317 to 1.104)	0.538 (-0.018 to 1.243)
	RURE	-0.178 (-0.476 to 0.231)	-0.077 (-0.757 to 0.053)	-0.423 (-0.629 to -0.064)
LV base Err	FORCE	-0.196 (-0.528 to 0.214)	-0.117 (-0.741 to 0.202)	-0.388 (-0.620 to 0.100)
	FORMED	-0.034 (-1.097 to 0.381)	0.593 (0.050 to 2.005)	0.734 (0.015 to 0.989)
	RURE	-0.117 (-0.349 to 0.109)	-0.184 (-0.485 to 0.055)	-0.305 (-0.580 to 0.091)

Table 4-2: Hodges-Lehmann estimates of median differences and 95% confidence intervals between different groups of canines for the three metrics of LV dyssynchrony: RURE, FORCE and FORMED for LV Err in mid-ventricular and basal slices.

Properties of PCA-based LV dyssynchrony metrics

In this analysis, two different approaches to PCA analysis are presented, each with their own advantages, and demonstrate that both effectively distinguish dyssynchrony and synchrony. While the PCA-based metrics were calculated for mid-ventricular and basal LV E_{cc} and E_{rr}, all future discussions about these metrics refer to mid-ventricular and basal LV circumferential strains due to sub-optimal performance of these metrics based on LV radial strains as discussed in the previous section. The FORCE parameter ranges from 0-1 like the FT-based CURE parameter, and lower values indicate greater dyssynchrony. In contrast, the FORMED parameter has a lower bound of 0 without a predefined upper bound, and higher values indicate more dyssynchrony. FORCE has the desirable property that there is minimal individual variance in the case of synchrony, with values very close to 1 for both normal animals and heart failure animals with a narrow QRS.

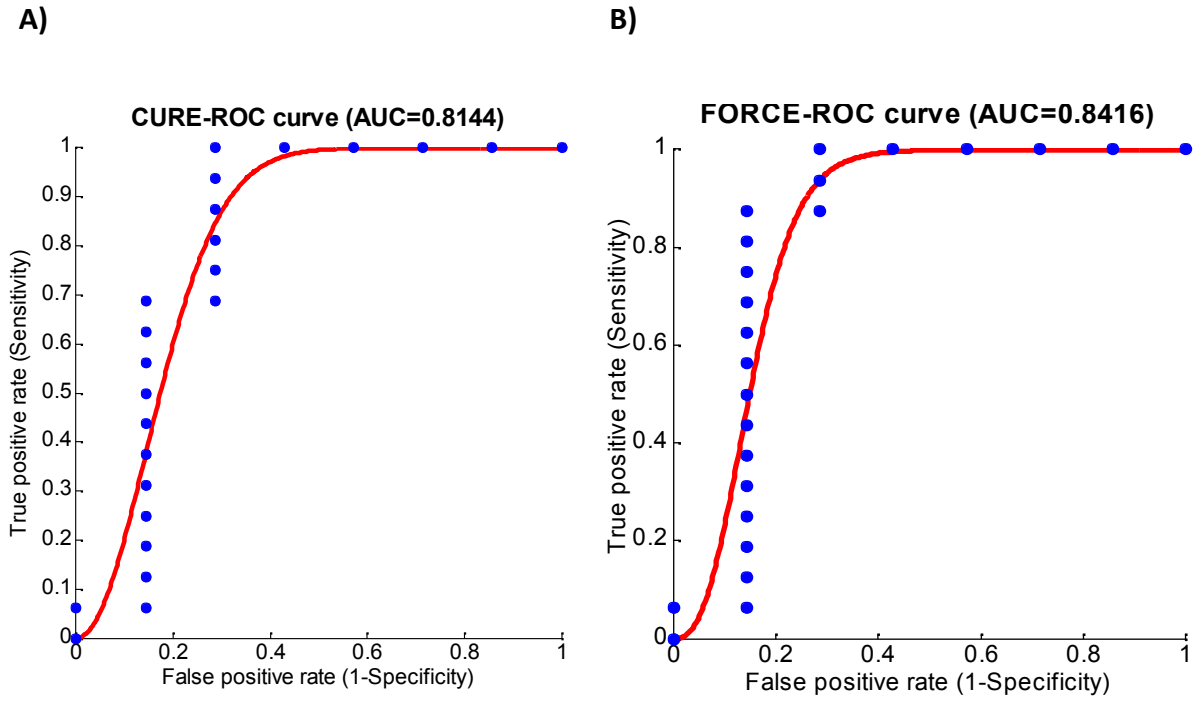
There is more variance in FORCE for dyssynchronous animals, as expected, due to inter-individual differences in regional LV contraction patterns. With respect to FORMED (PCA in time), there is also a marked difference in this parameter for animals with dyssynchrony compared to those with synchrony, with more individual variation in synchronous heart failure and normal animals.

4.1.b. PCA-based measures of LV dyssynchrony in heart failure patients (clinical CRT trial)

These promising results and advantageous properties of principal component analysis for quantifying LV dyssynchrony in canines merit further study of this methodology in patients

with clinical HF referred for CRT. Preliminary results on using FORCE and FORMED to improve CRT patient selection justify the development of new LV dyssynchrony metrics.

In Chapter 3, sensitivity and specificity were calculated for a 23-patient subset of patients referred to CRT with cutoffs of CURE<0.7, FORCE<0.795 or FORMED>0.9 indicating LV dyssynchrony. A more-detailed analysis of sensitivity and specificity for a range of different cutoffs is shown below using ROC analyses. ROC curves plot sensitivity (true positive rate) against 1-specificity (false positive rate). For an ideal classifier, the sensitivity is always 1 regardless of the specificity and hence a measure of the area under the ROC curve is a good indicator of the ability of the classifier to correctly identify positive and negative outcomes. The ROC curves for CURE, FORCE and FORMED are shown below in Figure 4-3, where the blue circles indicates true positive and false positive rates for all possible metric thresholds and the red lines indicate the ROC curve fits for which area under the ROC Curve (AUC) is calculated :



C)

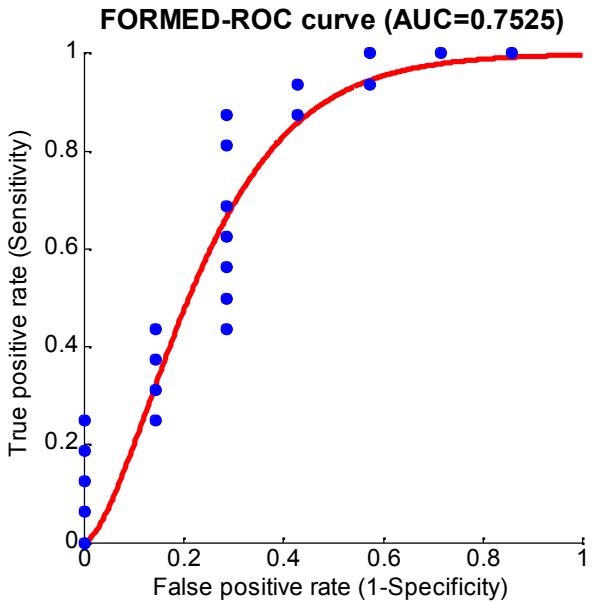


Figure 4-3: ROC curves (Sensitivity vs (1-Specificity)) indicating ability of the following LV dyssynchrony metrics to identify HF patients expected to have a positive CRT response: A) CURE, B) FORCE and C) FORMED

As we can see above, FORCE has the highest AUC with details shown below in Table 4-3:

	CURE	FORCE	FORMED
Area under ROC curve	0.81438	0.84157	0.75252
Standard Error	0.0903	0.08305	0.10438
95% Confidence Interval	[0.63740, 0.99137]	[0.67880, 1.00000]	[0.54795, 0.95710]
1-tail p-value ($p<0.05$ implies area under ROC is statistically greater than 0.5)	0.0002	$1.9531*10^{-5}$	0.0078

Table 4-3: Statistical ROC analysis indicating ability of the LV dyssynchrony metrics CURE, FORCE and FORMED to identify HF patients expected to have a positive CRT response

A 1-tailed t-test was performed to test that area under the ROC curve> 0.5 and p-values were <0.05 for all three metrics indicating that CURE, FORCE and FORMED are able to predict CRT response better than what would be expected by chance.

FORCE has both the highest area under the ROC curve and the lowest standard error (of area under ROC curve) indicating its ability to accurately predict CRT response in comparison with FORMED and CURE. However the area under the ROC curve is only slightly greater for FORCE (0.8416) compared to CURE (0.8144) and both are far more objective measures of LV dyssynchrony than typical time to peak E_{cc} measures of LV dyssynchrony using echocardiography.

Nevertheless, the dependence of FORCE on raw strain data without any curve fitting and its time-independence make it a more objective measure of LV dyssynchrony than CURE. Moreover, FORCE does not require selection of systolic frames for time-averaging making it user-independent as well unlike CURE. As a result, FORCE may be the ideal metric for selection of CRT patients and its success in canine studies and preliminary clinical trials warrants further investigation of its effectiveness at quantifying LV dyssynchrony.

4.2 Conclusions

LV dyssynchrony in Canine model of HF

PCA-based quantification of mechanical LV dyssynchrony from regional myocardial circumferential strains is feasible and provides a completely data-driven and time-independent methodology for determination of regional mechanical LV dyssynchrony. On the other hand,

PCA-based metrics are not as effective on radial strains since strains measured in this direction using cine DENSE MRI are not accurate. The PCA parameters FORCE and FORMED provide comprehensive assessments of regional strain throughout the LV and throughout the cardiac cycle in a canine model of HF. These PCA parameters are highly effective in distinguishing mechanical dyssynchrony from mechanical synchrony in a physiologic animal model of heart failure.

FORCE, in particular, has a very low inter-individual variance in canines with LV synchrony (heart failure or normal) and high inter-individual variance in canines with LV dyssynchrony making it very effective in identifying LV dyssynchrony. FORMED on the other hand has a relatively large inter-individual variance in all subjects. Also, FORCE and FORMED are able to identify LV dyssynchrony from LV E_{cc} with accuracy similar to that of CURE but with less user subjectivity due to their time-independence properties.

Since FORCE is being tested in a model of LBBB-HF in canines (severe LV dyssynchrony), CURE and FORCE appear to be equally effective in identifying LV dyssynchrony. However, in the context of CRT where patient selection is determined by a cutoff value for the LV dyssynchrony parameter the time-independence and objectivity of FORCE are invaluable towards optimal CRT patient selection. Considering that effective identification of CRT responders is of major public health significance in the treatment of heart failure, these findings merit further application of LV dyssynchrony quantification using FORCE, FORMED and CURE in patients referred for CRT, the preliminary results of which have been described in earlier chapters.

LV dyssynchrony as a criterion for CRT patient selection

A comparison of FORCE, FORMED and CURE in patients referred for CRT indicates superior ability (area under ROC curve) of FORCE to distinguish between patients with LV synchrony and LV dyssynchrony. This improvement in LV synchronicity classification would help to reduce the non-response rate in current CRT trials. Also, assessment of dyssynchrony using PCA-based metrics such as FORCE derived from cine DENSE MRI circumferential strain is feasible and predicts CRT response better than echo speckle tracking [27]. Finally, integration of CURE with other electromechanical parameters (e.g. QRS duration) and other imaging modalities (e.g. 3D echocardiography) has also been shown to be successful in predicting CRT response/non-response and CRT outcomes [28,29].

Clinical applications of LV dyssynchrony quantification to evaluation of CRT response

Mechanical dyssynchrony is just one determinant of CRT response but it has been shown to directly correlate with positive CRT response [30].

As shown from previous studies, assessment of CRT response is complex. Factors influencing CRT nonresponse can be divided into three categories: 1) underlying myocardial substrate (eg, presence of mechanical dyssynchrony and regional distribution of nonviable myocardium), 2) CRT implementation (lead placement and programming), and 3) patient-specific factors [31].

With respect to the first category of CRT response effects, the extent of mechanical LV dyssynchrony as obtained from PCA of regional MR strains could be integrated with information about myocardial scar at the time of the initial CRT study to predict CRT response. Although

PCA was performed on cine DENSE MRI strain data in this study, this methodology could be easily applied to strain data from other CMR methods and imaging modalities such as myocardial tagging, phase contrast velocity encoding and echocardiography. The above PCA-based methods for quantifying LV dyssynchrony from image-based LV strains, when combined with current criteria for CRT patient selection [12, 32, 33], will enable more accurate identification of patients with LV dyssynchrony that will receive the maximum benefit from CRT.

4.3 Future work

Improvements can be made to FORCE and FORMED by incorporating higher-order principal components, i.e. principal components with lower singular values, into the calculation of LV dyssynchrony metrics. Also, FORCE and FORMED can be combined with other electromechanical factors for optimal CRT patient selection and can be applied to strains from other imaging modalities such as echocardiography to better understand the relation between LV dyssynchrony and CRT patient response. Clinical CRT trials with large sample sizes of >100 patients could better elucidate the abilities of FORCE and FORMED to reduce CRT non-response rate. Finally, improved methods for determination of LV strains and 3D cine DENSE MRI can provide more accurate measures of LV mechanics resulting in improvements in LV dyssynchrony quantification.

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