PROPERTIES AND OPTIMIZATION OF RESPIRATORY NAVIGATOR GATING FOR SPIRAL CINE DENSE CARDIAC MRI

DISSERTATION

A dissertation submitted in partial fulfillment of the requirements of the degree of Doctor of Philosophy in the College of Engineering

at the University of Kentucky

By

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ABSTRACT OF DISSERTATION

PROPERTIES AND OPTIMIZATION OF RESPIRATORY NAVIGATOR GATING FOR SPIRAL CINE DENSE CARDIAC MRI

Cardiac magnetic resonance (CMR) can non-invasively assess heart function. Displacement encoding with stimulated echoes (DENSE) is an advanced CMR imaging technique that measures tissue displacement and can be used to quantify cardiac mechanics (e.g. strain and torsion). When combined with clinical risk factors, cardiac mechanics have been shown to be better predictors of mortality than traditional measures of function. End-expiratory breath-holds are typically used to minimize respiratory motion artifacts. Unfortunately, requiring subjects to breath-hold introduces limitations with the duration of image acquisition and quality of data acquired, especially in patients with limited breath-holding ability. Thus, DENSE acquisitions often require respiratory navigator gating, which works by measuring the diaphragm during normal breathing and only acquiring data when the diaphragm is within a pre-defined acceptance window.

Unfortunately, navigator gating results in long scan durations due to inconsistent breathing patterns. Moreover, the respiratory navigator configuration directly affects image quality. Scan duration and image quality need to be optimized in order to improve the clinical utility of DENSE. Thus, the goal of this project was to optimize those parameters. To accomplish this goal, we set out to 1) understand how respiratory gating affects measures of cardiac mechanics, 2) determine the optimal respiratory navigator configuration, and 3) reduce scan duration by using an interactive videogame.

Aim 1 of this project demonstrated that the variability in torsion, but not strain, could be significantly reduced through the use of a respiratory navigator compared to traditional breath-holds. Aim 2 of this project demonstrated that, among the configuration options, the dual-navigator configuration resulted in the best image quality compared to gold standard traditional breath-holds, but also resulted in the longest scan duration. Aim 3 demonstrated that using an interactive breathing- controlled videogame during CMR can significantly reduce scan duration compared to traditional free-breathing.

In summary, respiratory navigator gating with DENSE 1) reduces the variability in measured LV torsion, 2) results in the best image quality with the dual-navigator configuration, 3) results in significantly shorter scan durations through the use of an interactive videogame. Selecting the optimal navigator configuration and using an interactive videogame can improve the clinical utility of DENSE.

KEYWORDS: Respiratory Navigator Gating, Cardiac Magnetic Resonance Imaging, Displacement Encoding with Stimulated Echoes, Cardiac Mechanics, Interactive Videogame

Sean Michael Hamlet

Today’s Date

Date

PROPERTIES AND OPTIMIZATION OF RESPIRATORY NAVIGATOR GATING FOR SPIRAL CINE DENSE CARDIAC MRI

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To Regina

Once again, I could not have done this without your love and support.

Thank you for your continuing positivity and encouragement.

ACKNOWLEDGMENTS

Although this research was completed with my individual effort, its progress could not have been completed without the efforts of several people.

Paragraph 2

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**CHAPTER 1**

**BACKGROUND**

**1.1 Heart Disease**

Heart disease is the leading cause of death for both adult men and women [1]. The term ”heart disease” can refer to conditions that involve narrow or blocked blood vessels, which can lead to a heart attack, or conditions that affect the heart muscle, valves, or rhythm, which can lead to inefficient pumping and heart failure [1]. In addition to adults, there are children who are born with congenital heart disease (CHD), heart defects that can be present at birth, and it’s a growing problem that affects over 2 million people in the US [2]. As surgical and treatment techniques have improved, children with CHD are living to adulthood. For both adults and children, in order to develop improved techniques for treatment and therapy, heart disease and cardiac function need to be accurately monitored.

**1.2 Standard Cardiac Magnetic Resonance Imaging (MRI) and**

**Traditional Measures of Cardiac Function**

Magnetic resonance imaging (MRI) is a non-invasive non-ionizing medical imaging technique that is used to assess the function and health of internal structures of the human body. MRI involves the use of strong magnetic fields and radio waves along with the natural hydrogen nuclei, which are abundant in human tissue, to generate images. Thus, MRI can be used to non-invasively assess the cardiac function and health.

Non-invasive imaging has become standard protocol for diagnosis, prognosis, and management of heart diseases and for monitoring cardiac health. Traditional measures of cardiac function, such as ventricular volumes, ventricular mass, and ejection fraction, can be derived from standard cardiac MRI. Whole heart function

40 p<0.001

χ2 (for predicting mortality)

30 p=0.040

Clinical

Clinical + Ejection Fraction

20 Clinical + Longitudinal Strain

10

0 \*Data from Stanton et al; Circ Imaging 2009; 2:356-64

**Figure 1.1: Measuring cardiac strains dramatically improves the ability to predict mortality.**

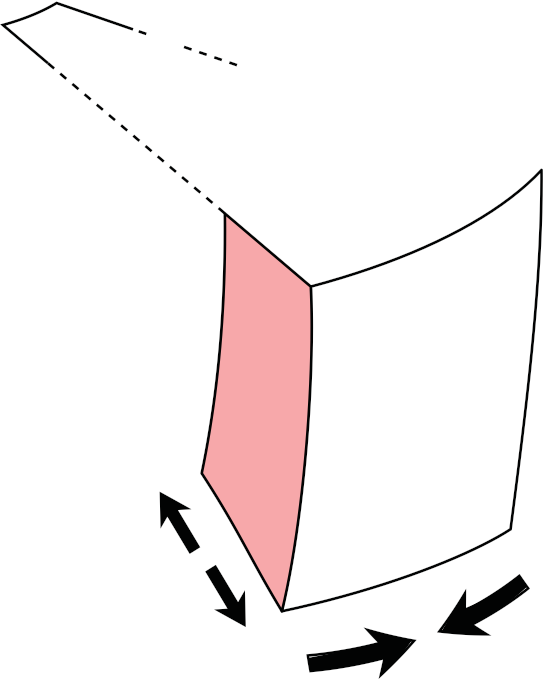
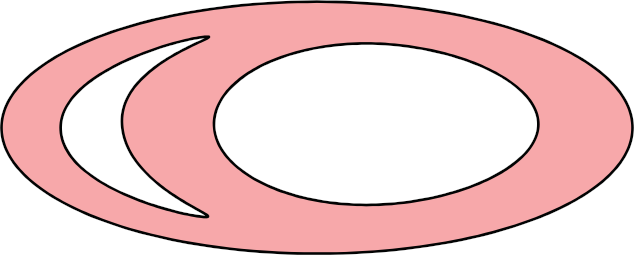
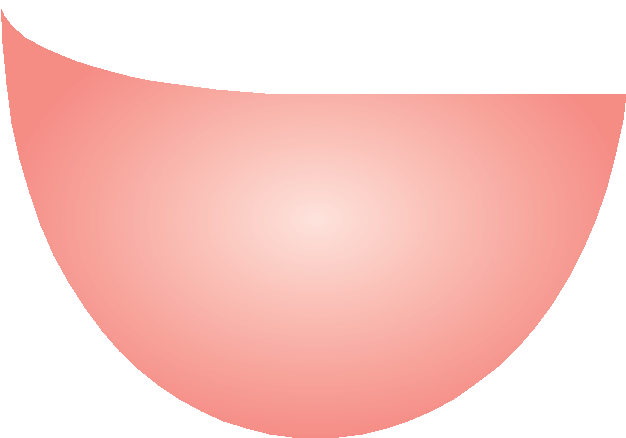
is typically assessed with these traditional metrics, but unfortunately, they may not contain enough information to explain the complex nature of some heart diseases. Moreover, there is a growing body of evidence that suggests that, when combined with clinical risk factors (e.g. hypertension), advanced measures of cardiac mechanics (e.g. cardiac strains and torsion) are better predictors of mortality compared to traditional measures [3] (Figure 1.1).

**1.3 Advanced Measures of Function: Cardiac Mechanics**

Cardiac mechanics, such as strain and torsion, measure the deformation of the heart as it contracts and relaxes throughout the cardiac cycle. Commonly measures directions include circumferentially, radially, and longitudinally (Figure 1.2). Torsion measures the twisting motion of the heart along the longitudinal axis of the heart throughout the cardiac cycle. Cardiac mechanics can be quantified from analyzing the motion of small regions of the heart, which can be completed by using an advanced imaging technique called spiral cine Displacement ENcoding with Stimulated Echoes (DENSE).

A: Cardiac Strain

−



Circumferential Strain (%)

−

**Figure 1.2: Cardiac strain is a measure of how small segments of the myocardium shorten or lengthen during contraction and relaxation.**

**1.4 Displacement Encoded Cardiac MRI**

Spiral cine Displacement ENcoding with Stimulated Echoes (DENSE) is an advanced cardiac magnetic resonance imaging technique that directly encodes the displacement of the myocardial tissue into the phase of the MR signal [4]. Because of its quantitative nature, as opposed to qualitative such as in standard cardiac MRI, it allows for simple and accurate quantification of cardiac mechanics. In addition, DENSE has good spatial resolution and good reproducibility [5, 6].

**1.5 Respiratory Motion and Blurring**

As with most cardiac MRI techniques, images are typically acquired using end- expiratory breath-holds. Breath-holds are used to suspend respiration so the bulk motion of the heart is minimized during imaging. Respiratory compensation is in order to reduce motion blurring in images (Figure XX). DENSE acquisitions are generally performed using end-expiratory breathholds ( 1520 s in duration) [cite 410]; however, this approach is constrained by the patients ability to breath- hold, which is limited in young subjects and many stages of advanced heart disease. Furthermore, short acquisitions preclude the ability to capture more robust data, such as three- dimensional (3D)DENSE,7,11,12 or high resolution imaging.13. In order to overcome this time limitation, a respiratory navigator has been used which allows the subject to breathe freely throughout image acquisition [cite].

**1.6 Respiratory Navigator Gating**

Respiratory navigator gating works by measuring the diaphragm position during normal breathing and only acquiring data when the diaphragm is within a pre-defined acceptance window (Figure XX). The trade-off of navigator gating is significantly increased scan duration because of poor navigator efficiency. For example, previous CMR studies have reported respiratory navigator efficiencies of 20 to 45% in adults

[47]. This poor navigator efficiency lengthens the duration of currently used clinical imaging and limits clinical feasibility of emerging advanced imaging techniques.

Now talk about how this time limitation can be fixed

Navigator efficiency is typically poor because breathing patterns can be erratic [810] and the patient is gener- ally unaware of the desired acceptance window location. Providing the patient with visual feedback of the dia- phragm position during CMR (navigator feedback)has been shown to improve breathing consistency and scan efficiency in adults [5, 8]. For example, studies have shown efficiency improvements up to 29

Moreover, there are different navigator configurations possible, which all affect navigator efficiency and image quality due to their distinct advantages and disadvantages.

Previous studies using navigator-gated DENSE have reported using a prospective single navigator configura- tion.7,12 However, there has been no formal comparison of the available navigator configurations. Moreover, the accuracy of derived cardiac mechanics and overall image quality for these navigator configurations compared with breathhold acquisitions as a reference standard are largely unknown. The purpose of this study was to determine the optimal configura- tion of respiratory navigator gating for the quantification of left ventricular strain using spiral cine DENSE MRI

**1.7 Dissertation Outline**

The goal of this project was to optimize respiratory navigator gating, which would improve the clinical utility of DENSE. To accomplish this goal, we set out to

1) understand how respiratory gating affects measures of cardiac mechanics, 2) determine the optimal respiratory navigator configuration, and 3) improve navigator efficiency, which reduces scan duration, by using an interactive breathing-controlled videogame during cardiac MRI.

In Chapters 2 and 3, we address the effects of inconsistent end-expiratory

diaphragm position between breath-holds and respiratory navigator gating on DENSE-derived cardiac mechanics, such as left ventricular strain and torsion. In Chapter 2, we learn that cardiac strain is insensitive to normal changes in end-expiratory position between breath-hold DENSE acquisitions. In Chapter 3, we discover that use of a respiratory navigator has the ability to significantly reduce the variability of cardiac torsion and thus the sample size needed to detect small changes in torsion. The conclusions of the studies performed for Chapters 2 and 3 demonstrate the importance of employing a respiratory navigator or some form of consistent respiratory compensation for future studies.

In Chapter 4, we address the optimal navigator configuration.

**CHAPTER 2**

**EFFECTS OF PATIENT-SPECIFIC VARIABILITY IN INCONSISTENT END-EXPIRATORY DIAPHRAGM POSITION ON THE QUANTIFICATION OF LEFT VENTRICULAR CARDIAC STRAINS**

*Adapted from...*

**2.1 Synopsis**

**Purpose:** To determine if normal inconsistency in end-expiratory diaphragm position between separate image acquisitions significantly affects estimates of cardiac strains. **Materials and Methods:** We enrolled 17 subjects, including seven patients with heart disease. For each subject, we measured the range of end-expiratory positions during 10 separate breath-holds. The imaging protocol comprised two ventricular long-axis and three short-axis slices of navigator-gated 2D cine displacement encoding with stimulated echoes (DENSE) cardiac magnetic resonance (MR). To simulate end-expiratory position inconsistency, DENSE images were each acquired at the patient-specific minimum, middle, and maximum end-expiratory positions; a repeated acquisition at the middle position was used to quantify variability independent of end-expiratory differences. Differences and variability of left ventricular peak strains were compared using analysis of variance and Students t-test.

**Results:** The range of end-expiratory positions across 10 breath-holds was

10 *±* 4 mm. There were no significant differences in global or regional peak radial, circumferential, or longitudinal strains measured at the different end-expiratory positions (p = 0.17–0.98). In general, there were also no differences in variability in global or regional peak strains between inconsistent (minimum, middle, and

maximum) and consistent (two acquisitions from middle position) end-expiratory positions (p = 0.10–0.95). With at least 80% power, the study had an ability to detect global differences of 4.7%, 1.0%, and 1.7% (absolute) between end-expiratory positions for radial, circumferential, and longitudinal strains, respectively. **Conclusion:** Measurements of left ventricular peak strains with DENSE cardiac MR are relatively insensitive to normal changes in end-expiratory position between separate image acquisitions.

**Keywords:** Cardiac Strains, Breath-holds, DENSE, Respiratory Navigator Gating

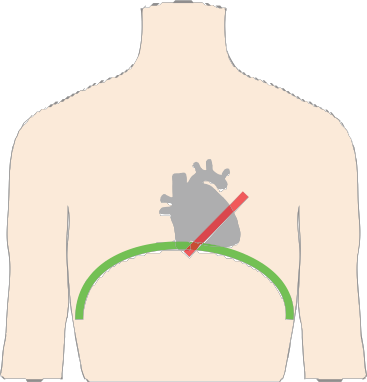
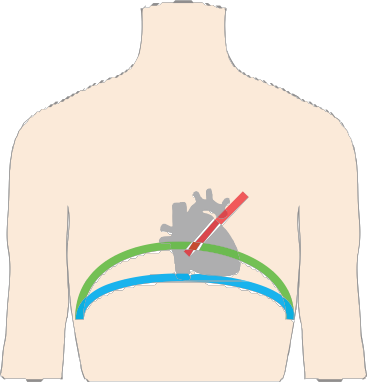
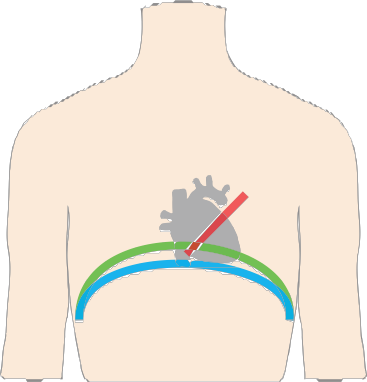
**2.2 Background**

Cardiac strains describe the deformation of myocardial tissue during contraction and relaxation. Measures of cardiac strains have been shown to be superior predictors of outcomes, such as mortality, compared to traditional measures of cardiac function or traditional clinical risk factors alone [3]. Imaging can non-invasively assess cardiac strains using echocardiographic techniques such as speckle tracking [7] and cardiovascular magnetic resonance (MR) techniques such as myocardial feature tracking [8], myocardial tissue tagging [9, 10], phase velocity mapping [11], strain encoding [12], and displacement encoding with stimulated echoes (DENSE) [4, 13].

Peak strains vary longitudinally throughout the left ventricle [14, 15, 16, 17, 18, 19, 20]. For example, previous studies have shown that left ventricular radial, circumferential, and longitudinal strains vary between the base and apex by up to 14%, 5%, and 5% (absolute), respectively [14, 15, 16, 17, 18, 19, 20]. Cardiac MR images are often acquired during end-expiratory breath-holds to minimize respiratory motion artifacts. However, it is often difficult to achieve consistency in end-expiratory diaphragm position between successive breath holds, and variations of 4 to 13 mm are normal [21, 22, 23, 24, 25]. Inconsistent end-expiratory positions will impact the position of the heart with respect to the imaging plane (Figure 2.1). For example, previous studies have reported short-axis and long-axis through-plane displacements of up to 14 mm due to displacement of diaphragm position between breath-holds [26, 27], and other studies have reported that the superior/inferior position of the heart can displace

55-92% of the displacement of the diaphragm position [28, 29]. Because peak strains vary throughout the left ventricle, we hypothesize that translation of the heart with respect to the imaging plane to result in differences and variability in measured strains.

End-Expiration Mid-Inspiration End-Inspiration



Cardiac Imaging Plane Original Diaphragm Position Current Diaphragm Position

**Figure 2.1: During respiration, diaphragm motion causes the heart to translate a significant distance while the imaging plane remains fixed.**

To our knowledge, no study has evaluated the sensitivity of cardiac strains to natural end-expiratory position variability. This is an important knowledge gap, especially since the use of cardiac strains is increasing dramatically both in research and clinical practice. The purpose of this study was to determine if normal inconsistency in end-expiratory position significantly affects the quantification of cardiac strains and therefore results in higher variability in measured cardiac strains compared to strains measured at a consistent end-expiratory position.

**2.3 Methods**

*2.3.1 Subjects*

The study protocol was approved by the local Institutional Review Board. Ten healthy volunteers with no known cardiovascular disease or chronic illnesses and 7 patients with a history of heart disease (known diagnosis of heart failure, cardiomyopathy, or myocardial infarction) provided written informed consent. Image acquisitions were performed on a 3T Siemens Tim Trio (Siemens Healthcare, Erlangen, Germany) scanner with a 6-element chest coil and a 24-element spine coil.

Coronal Localizer Image

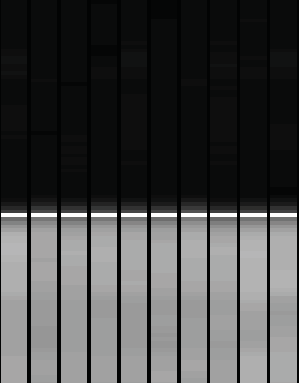
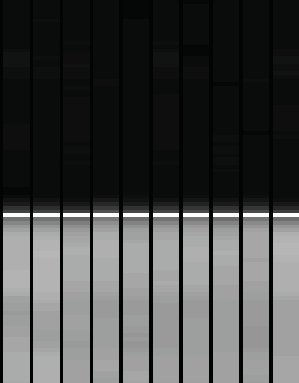
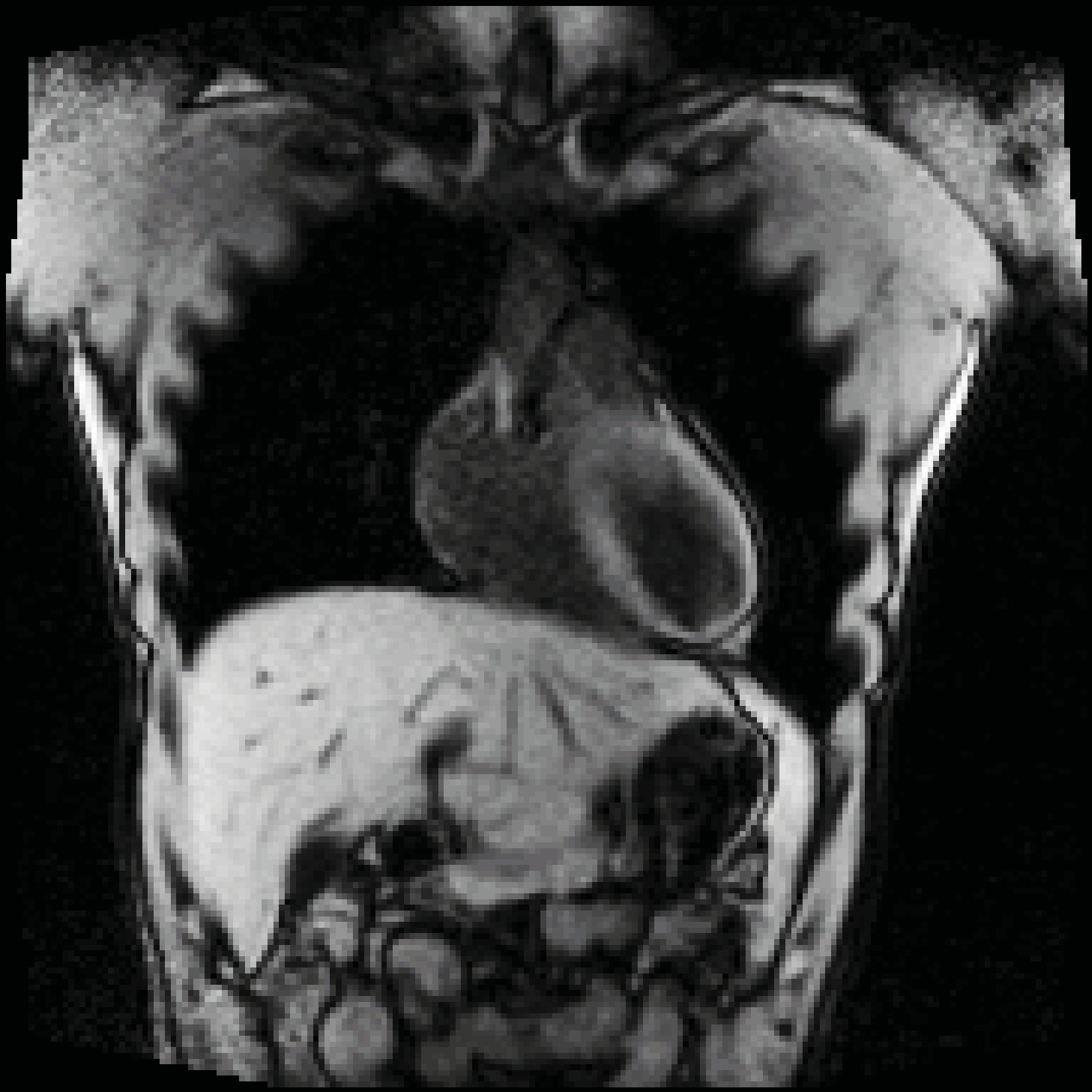


Image of Respiratory Navigator

(during breath-hold)

Lung

Exhale

Inhale

Detected Diaphragm Location

Liver

Time

**Figure 2.2: Respiratory navigator gating.** (Left) The diaphragm position was measured at the high-contrast interface between the lung (dark) and the liver (bright). (Right) Image of a measured diaphragm position over time during a breath-hold.

*2.3.2 Quantification of Inconsistent End-Expiratory Positions*

To determine the inconsistency in end-expiratory positions for each subject, a respiratory navigator sequence measured the diaphragm position (Figure 2.2) during

10 consecutive breath-holds. During each breath-hold, the diaphragm position was imaged three times per second over a period of 10 seconds for 30 total measurements. No cardiac image data were collected during these acquisitions. The mode of the

30 diaphragm positions defined the measured end-expiratory position of that breath- hold. The patient-specific minimum, middle, and maximum end-expiratory positions were defined from the series of 10 breath-holds (Figure 2.3).

*2.3.3 DENSE Acquisition*

For each subject, navigator-gated 2D spiral cine DENSE in 2-chamber and

4-chamber long-axis and basal, mid-ventricular, and apical short-axis orientations of the left ventricle were acquired four times. Specifically, all image orientations were

Measured

Defined Patient-Specific End-Expiratory Positions

End-Expiratory Positions

Relative

Position (mm)

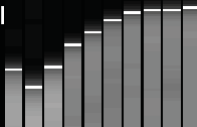
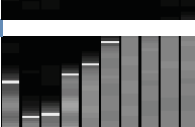
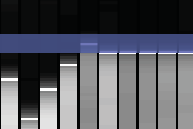
10

Minimum

Middle

Maximum

0



Exhale

-10

1 Breath-hol 10

d

Inhale

Number

**Figure 2.3: A respiratory navigator was used to measure end-expiratory positions to define the patient-specific minimum, middle, and maximum end-expiratory positions.** The minimum position was defined as being closer to the end-inspiratory position while the maximum position was defined as being closer to the end-expiratory position.

acquired with the navigator acceptance window prescribed at the patient-specific maximum and minimum end-expiratory positions, and twice in the middle position to quantify variability in strain independent of end-expiratory position variability (Figure 2.3). A navigator feedback system, which used an angled mirror and projector screen placed at the back of the scanner bore, was used to facilitate quicker acquisitions by enabling subjects to view the navigator acceptance window position in real-time during image acquisition [30]. For each end-expiratory position, all image orientations were acquired within a single navigator-gated scan.

Prospective ECG gating was used during DENSE acquisitions. The number of cardiac phases ranged from 31 to 49 and varied based on subject heart rate. Additional DENSE imaging parameters included: spiral interleaves = 6, FOV = 360x360 mm2, pixel spacing = 2.8x2.8 mm2, slice thickness = 8 mm, TE =

1.1 ms, TR = 17 ms, variable flip angle = 20*◦*, displacement encoding = 0.06

cyc/mm [6], through-plane dephasing = 0.08 cyc/mm [31], CSPAMM echo suppression [32], and view sharing. A dual-navigator strategy was used, requiring the diaphragm to be within the navigator acceptance window (*±*3 mm) both before

and after the data acquisition during each R-R interval [33].

*2.3.4 DENSE Post-Processing*

DENSE image data were analyzed using the open-source software, *DENSEanalysis* [34]. For each image orientation, the left ventricular myocardium was manually delineated using epicardial and endocardial contours and an end-diastolic and end-systolic cardiac phase [35]. Post-processing and segmentation were performed as described by Suever et al. [35]. Seed points indicating unwrapped phase data were manually selected, and a path-following algorithm was used to unwrap the displacement-encoded phase data. The resulting displacement trajectories were further processed by applying spatial smoothing and temporal fitting as previously described [36].

Two-dimensional Lagrangian strains were computed from the smoothed trajectories over the entire cardiac cycle. Radial and circumferential strains were computed from the short-axis images and longitudinal strain was computed from the long-axis images. Global peak strains were calculated by averaging the mean strain curves of all the myocardial segments and identifying the peak of the global mean curve. Regional peak strains were computed by averaging the strain curves from all the myocardial segments for a given region and identifying the peak of the regional curve. Segmental peak strains were computed by identifying the peak of the strain curve for each myocardial segment. For peak longitudinal strain computation, pixels within 10% of left ventricular longitudinal length from the most basal and apical regions were excluded because of the increased noise which is typically observed in the strain curves in those regions. Peak strain was defined as positive for thickening (radial) and negative for shortening (circumferential and longitudinal).

*2.3.5 Statistics*

Statistical analyses were performed using R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). All continuous variables were expressed as mean *±* standard deviation or range. Cardiac strains were tested for normality using a Shapiro-Wilk test.

To quantify mean differences in cardiac strains due to inconsistent end-expiratory positions (minimum, middle, and maximum positions), cardiac strains were compared between the patient-specific acceptance window positions using a two-way analysis of variance (ANOVA) with repeated measures with group (healthy vs patient) and acceptance window position as the independent factors. A Scheirer-Ray-Hare test was used for data determined to be non-normally distributed [37]. Using the results of the two-way ANOVA or Scheirer-Ray-Hare test, the interaction between group and acceptance window position on cardiac strains was determined. If there was no interaction between group and acceptance window position, the groups were combined and mean differences due to inconsistent end-expiratory positions were quantified by comparing cardiac strains between acceptance window positions using a one-way ANOVA with repeated measures with acceptance window position as the independent factor. A Friedman test was used for data determined to be non-normally distributed [37].

To quantify variability due to inconsistent end-expiratory positions, the standard deviations of strains were compared between the inconsistent positions (maximum, middle, and minimum) and consistent positions (two acquisitions at the middle position) using a Students t-test. For all statistical tests, significance was defined as p *<* 0.05. Bland-Altman analysis [38] was used to assess the reproducibility of each measurement using inter-test 95% limits of agreement defined using the two measurements from the middle position. Inconsistency in end-expiratory position across ten separate breath-holds for each subject was reported using both ranges

and standard deviations from the ten breath-holds, and these values were compared between patients and healthy controls.

Power analyses were performed to quantify the ability of this study to detect meaningful differences in strain between the different end-expiratory positions. Because repeated-measures ANOVAs were used to detect differences, and because equations for power are not readily available for repeated-measures ANOVA, simulations were performed to estimate power. Specifically, for each strain, 10,000 iterations were performed. For each iteration, strain values for the minimum end-expiratory position were randomly drawn from a normal distribution using the mean and standard deviation across the subjects measured in this study. The number of strain values drawn corresponded with the number of subjects (healthy and patients combined). For a given difference to detect, *δ*, values at the two other end-expiratory positions were calculated by adding *δ/*2 and *δ* to the values at the minimum position. Measurement variability was then added to those two end-expiratory positions by drawing random values from a normal distribution with zero mean and a standard deviation equal to the measured average standard deviation of the differences between any two positions. In this manner, each iteration simulated a mean difference of *δ* between the minimum and maximum breath-hold positions and included typical inter-test measurement variability. The percentage of iterations for which a repeated-measures ANOVA yielded a significant result (p *<* 0.05) was the estimate of power. The 95% confidence interval of that estimate was calculated from the normal approximation to the binomial distribution with N = 10,000. The values of *δ* that yielded at least 80% power were reported separately for global and regional strains.

**2.4 Results**

was excluded due to movement during imaging, so data from the remaining 9 healthy subjects are reported. Data from the basal and apical DENSE images of these subjects were previously used to assess the variability of left ventricular torsion [39].

*2.4.1 Inconsistent End-Expiratory Positions*

As previously reported [39], the average range of end-expiratory positions were not significantly different (p = 0.94) between the healthy (10.1 *±* 4.8 mm) and patient (10.3 *±* 4.2 mm) groups (total range of 4-19 mm). Since range is sensitive to outliers, the standard deviation of end-expiratory position was also compared between groups, and similarly there were no significant differences (3.1 *±* 1.3 mm vs 3.4 *±* 1.7 mm, p = 0.70) [39].

*2.4.2 Differences and Variability in Peak Strains*

There was no interaction between group (healthy vs patient) and navigator acceptance window position for peak strains (Table 2.1), thus the remaining analyses were performed with all subjects combined. Neither global, regional, nor segmental peak strains were significantly different as a function of acceptance window position (Table 2.1; Tables A.1 and A.2 in Supplemental). Moreover, the differences in mean strain between any two acceptance window positions were each smaller than their corresponding inter-test 95% limits of agreement (Table 2.1). For example, mean global circumferential strain across acceptance window positions ranged from -16% to -17%; the difference was 1%, which is smaller than the corresponding inter-test 95% limits of agreement of *±*1.7% (Table 2.1). Finally, the standard deviations in peak strains were not significantly different between inconsistent (minimum, middle, and maximum) and consistent (repeated measurements at middle position) acceptance window positions for all subjects combined (Table 2.2). With at least 80% power, this study had the ability to detect strain differences of 4.7%, 1.0%, and 1.7% (absolute) between end-expiratory

**Table 2.1: Global and regional peak strains (mean standard deviation) from the three acceptance window positions (minimum, middle, and maximum) for all subjects combined.**

**Measurement**

Radial Strain (%)

**Acceptance Window Position**

**Minimum Middle Maximum**

**p-value***†* **95% LoA p-value***‡*

Global 29 *±* 12 29 *±* 12 30 *±* 13 0.95 *±*7.9 0.99

Base 37 *±* 15 35 *±* 14 37 *±* 14 0.95 *±*13.1 0.89

Mid-Ventricle 28 *±* 11 29 *±* 14 28 *±* 13 0.77 *±*10.4 0.51

Apex 26 *±* 12 27 *±* 10 29 *±* 16 0.78 *±*15.8 0.79

Circum. Strain (%)

Global -16 *±* 4 -17 *±* 4 -17 *±* 5 0.57 *±*1.7 0.65

Base -15 *±* 4 -15 *±* 4 -15 *±* 4 0.83 *±*3.6 0.71

Mid-Ventricle -16 *±* 4 -17 *±* 4 -17 *±* 4 0.17 *±*2.1 0.78

Apex -19 *±* 5 -19 *±* 5 -19 *±* 5 0.98 *±*4.6 0.93

Long. Strain (%)

Global -12 *±* 4 -12 *±* 3 -13 *±* 4 0.44 *±*3.2 0.48

2ch -13 *±* 3 -12 *±* 3 -13 *±* 4 0.94 *±*6.2 0.75

4ch -12 *±* 4 -13 *±* 4 -13 *±* 4 0.84 *±*4.1 0.38

*†*Results from test comparing acceptance window positions

*‡*Results from test comparing interaction between group (healthy vs patient) and acceptance

window position

positions for global radial, circumferential, and longitudinal strain, respectively

(Table 2.3). Additionally, this study had at least 80% power to detect differences of

8.9%, 2.2% and 2.6% for regional radial, circumferential, and longitudinal strain, respectively (Table 2.3).

**2.5 Discussion**

Quantification of cardiac strains typically requires a series of image acquisitions performed during end-expiratory breath-holds. This study explored the effects of inconsistent end-expiratory positions on the quantification of left ventricular cardiac strains. The results of the study showed that 1) inconsistent end-expiratory positions had minimal effect on the quantification of global and regional peak strains compared to inter-test variability for a given imaging location; and 2) the

**Table 2.2: Standard deviation of global and regional peak strains across inconsistent (maximum, middle, minimum) and consistent (middle and repeated middle) acceptance window positions.** Values reported as mean standard deviation.

**Measurement Acceptance Window Positioning p-value**

**Inconsistent Consistent**

Radial Strain (%)

Global 3.2 *±* 1.7 2.3 *±* 1.8 0.17

Base 4.9 *±* 2.5 3.5 *±* 3.3 0.18

Mid-Ventricle 4.3 *±* 2.5 2.5 *±* 2.8 0.10

Apex 5.7 *±* 4.1 4.3 *±* 3.9 0.16

Circumferential Strain (%)

Global 0.7 *±* 0.4 0.5 *±* 0.3 0.10

Base 1.0 *±* 0.5 1.1 *±* 0.7 0.41

Mid-Ventricle 0.7 *±* 0.3 0.6 *±* 0.5 0.55

Apex 1.4 *±* 0.9 1.4 *±* 0.9 0.95

Longitudinal Strain (%)

Global 1.1 *±* 0.7 0.8 *±* 0.9 0.27

2ch 1.4 *±* 1.1 1.5 *±* 1.6 0.89

4ch 1.4 *±* 1.6 1.2 *±* 0.9 0.72

**Table 2.3: Power analyses for studys ability to detect a difference in global and regional strain between different end-expiratory positions.**

**Measurement Power (%) Difference To Detect**

**(absolute, %)**

Radial Strain (%)

Global 80.9 *±* 0.8 4.7

Base 96.1 *±* 0.4

Mid-Ventricle 98.4 *±* 0.2

Apex 80.2 *±* 0.8

Circumferential Strain (%)

8.9

Global 80.5 *±* 0.8 1.0

Base 99.6 *±* 0.1

Mid-Ventricle 100 *±* 0.0

Apex 80.6 *±* 0.8

Longitudinal Strain (%)

2.2

Global 80.0 *±* 0.8 1.7

2ch 95.0 *±* 0.4 2.6

4ch 80.5 *±* 0.8

variability of global and regional peak strains was similar between inconsistent and consistent end-expiratory positions. Importantly, these findings provide assurance that the measurement of cardiac strains is relatively robust with respect to inconsistent end-expiratory positions.

Peak strains vary throughout the left ventricle. For example, we found that the magnitude of circumferential strain was 2% (absolute) higher in the apical region than the base–in agreement with previous studies [14, 15, 16, 17, 18, 19]–and radial strain was 9% (absolute) higher in the basal region than the apex. Due to these strain gradients, we hypothesized that the displacement of the heart due to motion of the diaphragm with respect to the imaging plane would create differences in measured strains. For example, we might expect that radial strains for the maximum end-expiratory position (i.e., maximal exhalation) would be lower in magnitude compared to the minimum end-expiratory position due to the heart being imaged more apically. We also might expect this to manifest as higher variability in strains across different end-expiratory positions compared to consistent end-expiratory positions. The likely explanation for finding that there is no difference in strains between end-expiratory positions is that, because the longitudinal axis of the heart (base to apex) is not necessarily perpendicular to the diaphragm plane, a 10 mm translation in the diaphragm position does not directly correspond with a 10 mm translation of the heart through the imaging plane.

Previous studies suggest that regions of the heart could displace at least 3 and possibly up to 14 mm through the fixed imaging plane between breath-holds [26,

27, 28, 29]. Our study had an average range of end-expiratory diaphragm position between breath-holds of approximately 10 mm, which is consistent with previous studies. Since the imaging slice thickness is 8 mm, even with a 14 mm through-plane displacement, there is likely not much difference in the acquired data from the imaged heart locations compared to the imaging plane location. Overall, since there were no

significant differences in peak global, regional, and segmental strains between end- expiratory positions, patient end-expiratory diaphragm position does not have to be monitored when performing breath-hold DENSE acquisition for single image analyses.

This studys goal was to quantify the effects of inconsistent end-expiratory positions on cardiac strains by computing the differences in strain between different end-expiratory positions. Thus, it was important for this study to detect meaningful strain differences between different patient-specific end-expiratory positions. This study had at least 80% power to detect global strain differences of 4.7%, 1.0%, and

1.7% and regional strain differences of 8.9%, 2.2%, and 2.6%, between different end-expiratory positions for radial, circumferential, and longitudinal strain, respectively. Importantly, the studys detectable difference was similar to or smaller than previously reported values of inter-test limits of agreement for circumferential strain and radial strain [6]. Notably, in some regions, the power to detect a meaningful difference was much higher (close to 100%) indicating that, in those regions, this study may have had the ability to detect even smaller than reported detectable differences.

We used DENSE to investigate our hypothesis that a patients normal variability in end-expiratory position between image acquisitions significantly affects the quantification of cardiac strains. DENSE was chosen to test our hypothesis because it has been previously shown to have good reproducibility [5], can be acquired in high spatial resolution [4, 13], and enables straightforward computation of cardiac strains. However, our findings should generalize to other image acquisitions that are used to derive measures of cardiac strains such as echocardiography, tagged MRI, etc.

We used respiratory navigator gating to acquire the DENSE cardiac images, which reduces respiratory artifacts during image acquisition, so we could not measure the effect of inconsistent end-expiratory position during breath-holds on

the derived strains. It would be beneficial to quantify the amount of end-expiratory position variability during breath-hold cardiac MR image acquisition and determine whether the magnitude of inconsistent end-expiratory positions correlates with changes in strain values. An example would be to explore whether inconsistent end-expiratory positions during a breath-hold DENSE scan causes blurring due to motion and results in lower strain magnitudes.

This study examined the effects of inconsistent end-expiratory positions on cardiac strains in a small patient sample. It would be beneficial to investigate this effect in a larger patient sample who have heterogeneous contraction patterns, for example, due to post-myocardial infarction. These patients may have steeper gradients in strain across infarcted to non-infarcted tissue regions [40]. Therefore, we cannot definitively say that the effects of inconsistent end-expiratory positions in that setting are similarly small and negligible. Future studies should investigate strain variability due to inconsistent end-expiratory positions in patients who have infarcted tissue in specific regions (e.g. anterior vs inferior).

In conclusion, the quantification of peak left ventricular cardiac strains is relatively insensitive to normal variations in end-expiratory positions between image acquisitions. Since there were no differences in peak strain between end-expiratory positions, patient end-expiratory diaphragm position does not have to be monitored when performing breath-hold DENSE acquisition for single image analyses. These findings should generalize to other image acquisitions that are used to derive measures of cardiac strains.

**CHAPTER 3**

**USING A RESPIRATORY NAVIGATOR REDUCES VARIABILITY WHEN QUANTIFYING LEFT VENTRICULAR TORSION**

*Adapted from Hamlet SM, Haggerty CM, Suever JD, Wehner GJ, Andres KN, Powell DK, Charnigo RJ, Fornwalt BK. Using a Respiratory Navigator Significantly Reduces Variability when Quantifying Left Ventricular Torsion with Cardiovascular Magnetic Resonance. Journal of Cardiovascular Magnetic Resonance. 2017. (in Press)*

The purpose of this work was to determine the effects of using a respiratory navigator on the variability of left ventricular torsion derived from spiral cine displacement encoding with stimulated echoes (DENSE) MRI. In this chapter, we discuss the two separate experimental protocols (using 1. *enforced* and 2. *natural* variability in end-expiratory position) used to test the hypothesis that high inter-test variability in left ventricular torsion is partly due to inconsistent breath-hold positions during serial image acquisitions, which could be significantly improved by using a respiratory navigator for cardiac MRI based quantification of left ventricular torsion.

**3.1 Synopsis**

**Background:** Left ventricular (LV) torsion is an important indicator of cardiac function that is limited by high inter-test variability (50% of the mean value). We hypothesized that this high inter-test variability is partly due to inconsistent breath- hold positions during serial image acquisitions, which could be significantly improved by using a respiratory navigator for cardiovascular magnetic resonance (CMR) based quantification of LV torsion.

**Methods:** We assessed respiratory related variability in measured LV torsion with

two distinct experimental protocols. First, 17 volunteers were recruited for CMR with cine displacement encoding with stimulated echoes (DENSE) in which a respiratory navigator was used to measure and then enforce variability in end-expiratory position between all LV basal and apical acquisitions. From these data, we quantified the inter-test variability of torsion in the absence and presence of enforced end-expiratory position variability, which established an upper bound for the expected torsion variability. For the second experiment (in 20 new, healthy volunteers), 10 pairs of cine DENSE basal and apical images were each acquired from consecutive breath-holds and consecutive navigator-gated scans (with a single acceptance position). Inter test variability of torsion was compared between the breath-hold and navigator-gated scans to quantify the variability due to natural breath-hold variation. To demonstrate the importance of these variability reductions, we quantified the reduction in sample size required to detect a clinically meaningful change in LV torsion with the use of a respiratory navigator.

**Results:** The mean torsion was 3.4*±*0.2 *◦*/cm. From the first experiment, enforced

variability in end-expiratory position translated to considerable variability in measured torsion (0.56*±*0.34 *◦*/cm), whereas inter-test variability with consistent

end-expiratory position was 57% lower (0.24*±*0.16 *◦*/cm, p*>*0.001). From the second

experiment, natural respiratory variability from consecutive breath-holds translated to a variability in torsion of 0.24*±*0.10 *◦*/cm, which was significantly higher than the

variability from navigator-gated scans (0.18*±*0.06 *◦*/cm, p=0.02). By using a

respiratory navigator with DENSE, theoretical sample sizes were reduced from 66 to

16 and 26 to 15 as calculated from the two experiments.

**Conclusions:** A substantial portion (22*−*57%) of the inter-test variability of LV torsion can be reduced by using a respiratory navigator to ensure a consistent breath- hold position between image acquisitions.

**Keywords:** Left Ventricular Torsion, Breath holds, DENSE, Respiratory Navigator

Gating, cardiovascular magnetic resonance

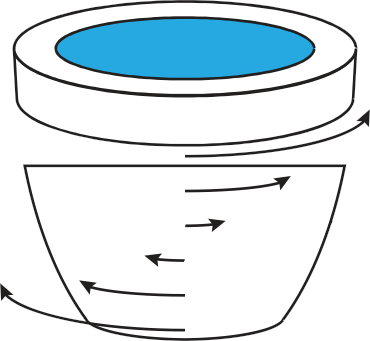
**3.2 Background**

Left ventricular (LV) torsion is an important indicator of cardiac function [41, 42]; however, the quantification of torsion is limited by poor inter-test reproducibility. For example, a previous study with myocardial tagging demonstrated that the inter-test variability of torsion represented nearly 50% of the mean value [19]. This substantial variability reduces prognostic value for individual patients and leads to larger required sample sizes for research studies to detect meaningful differences or changes. Previous studies have reported that sample sizes ranging from 80 107 are required to detect a

10% relative difference in torsion with 90% power [19, 43, 44]. Reducing variability and lowering required sample sizes is important to improve the clinical and research utility of torsion.

LV torsion is typically quantified as the gradient of twist along the longitudinal axis of the heart. This gradient is computed using twist derived from two short axis images (basal and apical) of the LV and the longitudinal distance between the images [19] (Figure 3.1). End-expiratory breath-holds are used to minimize respiratory motion artifacts, and the basal and apical short axis images are typically acquired during separate breath-holds. When post processing the image data to compute LV torsion, the longitudinal distance between the short axis images is calculated from either A) assumptions derived from an additional longitudinal image (echocardiography) or B) information specifying the location of the imaging planes in 3D space taken from the Digital Imaging and Communications in Medicine (DICOM) image header (cardiovascular magnetic resonance [CMR]). A confounding factor that is not considered is that the exact end-expiratory position may differ by up to 13 mm between separate breath-holds [21, 22, 23, 24, 25], which creates differences in heart position between the basal and apical image acquisitions (Figure 3.2). We hypothesized that inconsistent end-expiratory diaphragm positions during serial breath-holds accounts for a significant portion of the variability in

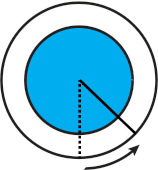
Base



Base

Apex

ϕb

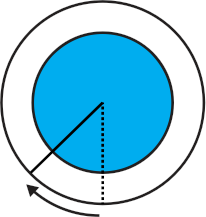


d

Apex ϕa

ϕ = ϕa - ϕb

ϕ



= d

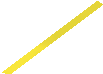
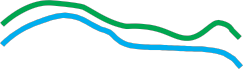
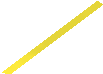
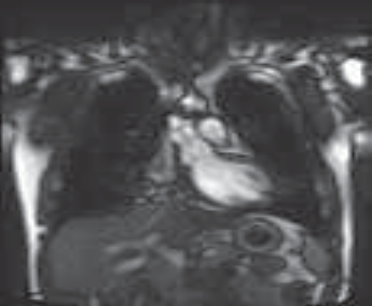
**Figure 3.1: Computation of LV torsion from basal and apical images.** The curved arrows represent the relative twist along the longitudinal axis of the left ventricle. LV twist (*φ*) was measured as the difference in rotation between the apex (*φa*) and base (*φb*) (twist direction shown as viewed from foot to head). Torsion *τ* was computed as LV twist divided by the distance (*d*) between basal and apical image locations.

measured LV torsion and that this variability could be reduced by using CMR based quantification of LV torsion with a respiratory navigator.

**3.3 Methods**

Respiratory related variability in measured LV torsion was assessed with two distinct experimental protocols: 1) using *enforced* variability in end-expiratory position between acquisitions and 2) allowing for *natural* variability in end-expiratory position between acquisitions. The former experiment was performed to establish an upper bound on respiratory related variability in torsion, while the latter mimics a more relevant clinical setting. In both experiments, the effect of using a respiratory navigator to ensure a consistent end-expiratory position on torsion variability was also quantified. The local Institutional Review Board approved the study protocols, and all subjects provided written informed consent.

Cardiac Imaging Plane



Original Diaphragm Position

Current Diaphragm Position

End-Expiration Mid-Inspiration End-Inspiration



**Figure 3.2: Real time images of the diaphragm as it translates during a respiratory cycle.** During respiration, diaphragm motion causes the heart to translate a substantial distance through the fixed imaging plane.

*3.3.1 LV Motion Quantification*

Imaging was performed on a 3T Siemens Tim Trio (Siemens Healthcare, Erlangen, Germany) with a 6 element chest coil and a 24 element spine coil. LV twist was measured at basal and apical short axis locations in both experiments using 2D spiral cine Displacement Encoding with Stimulated Echoes (DENSE) CMR [45, 46].

The basal and apical short axis locations were defined as follows: On a four chamber image, five short axis slices were planned equidistant across the end systolic endocardial ventricular long axis length. The slices were planned such that the outermost slices did not extend beyond the mitral valve plane and endocardial apex, respectively. The second and fourth slices of this stack were defined as the basal and apical short axis locations. Imaging parameters were: spiral interleaves = 6, interleaves per frame = 2, FOV = 360x360 mm2, pixel spacing = 2.8x2.8 mm2, slice thickness = 8 mm, TE/TR = 1.1/17 ms, temporal resolution = 34 ms, variable flip angle = 20*◦*, displacement encoding = 0.06 cyc/mm [6], through plane dephasing =

0.08 cyc/mm [31], CSPAMM echo suppression [32], view sharing, prospective ECG

gating, and a respiratory navigator with an acceptance window of *±*3 mm.

*DENSEanalysis* [34] was used to derive LV twist from the DENSE images. Epicardial and endocardial contours were manually delineated on the DENSE magnitude images at end-diastolic and end-systolic cardiac phases [35]. Post processing was performed as previously described [35]. A semi-automatic path following algorithm was used to unwrap the displacement encoded phase data. The resulting displacement trajectories were further processed by applying spatial smoothing and temporal fitting [36].

LV twist was computed over the cardiac cycle relative to the centroid of the endocardial boundary at end-diastole. The distance between the basal and apical image locations was calculated from the DICOM headers. LV torsion was computed as the difference in rotation between the apex and base (*φ*) divided by the distance (*d*) between the basal and apical image locations [19, 47, 48] (Figure 3.1).

*3.3.2 Experiment 1: Enforced End-Expiratory Variability*

Ten healthy volunteers with no known cardiovascular disease or chronic illnesses and seven patients with a history of heart disease (known diagnosis of heart failure, cardiomyopathy, or myocardial infarction) were recruited. We first quantified the end-expiratory variability for each subject by acquiring respiratory navigator measurements (90180 cross pair configuration; Figure 3.3) of 10 consecutive, 10 second breath-holds. No cardiac image data were acquired, but the mode position of each breath-hold was retained to identify subject specific minimum, middle and maximum end-expiratory positions of the diaphragm across the 10 breath-holds (Figure 3.4). These subject specific positions were then used to define the locations of the navigator acceptance windows for subsequent acquisitions of respiratory navigator-gated DENSE. Specifically, the basal and apical slices were both acquired with the navigator acceptance window at each of the three positions. Moreover, the acquisitions at the middle acceptance window location were repeated to define inter-test variability when ensuring a consistent position with a respiratory

Coronal Localizer

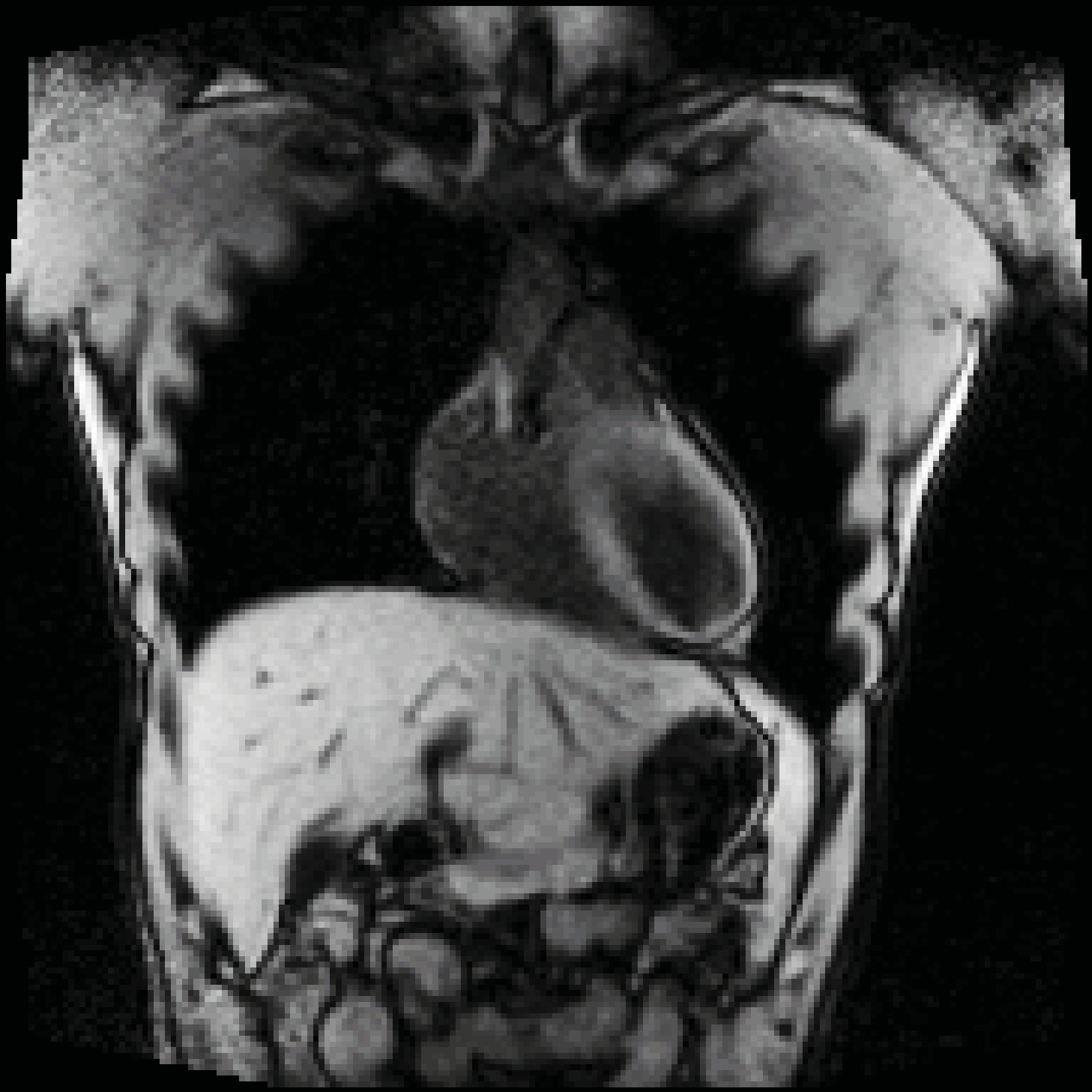
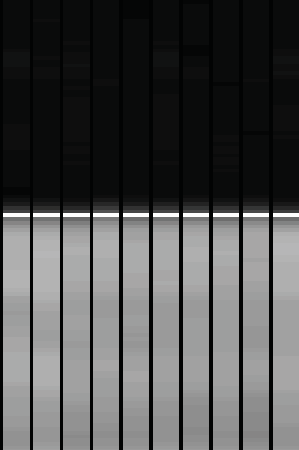
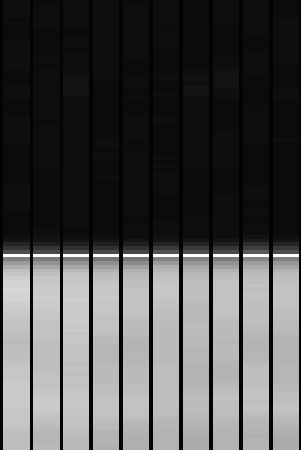


Image of Respiratory Navigator

Breath-hold 1 Breath-hold 10

Lung



Exhale

Liver

Detected Diaphragm Location

11mm

Time

Inhale

**Figure 3.3: Respiratory navigator gating.** (Left) The diaphragm position is at the high contrast interface between the lung (dark) and the liver (bright). (Right) Image of a measured diaphragm position over time for separate breath-holds. For this subject, there was an 11 mm difference in end-expiratory position between breath- hold 1 and 10.

navigator. For all scans, the image of the respiratory navigator was projected to the subjects in real time during DENSE acquisition, which helped to ensure consistent efficiency [33] across scans despite varying acceptance locations.

With three independent measurements at both LV locations, nine permutations of torsion were calculated from the possible combinations (Figure 3.5), providing an estimate of torsion variability due to inconsistent end-expiratory positions. This variability in torsion was compared to the inter-test variability (i.e., comparing the two torsion measures acquired at the middle navigator acceptance position, Figure 3.5) to isolate respiratory position effects.

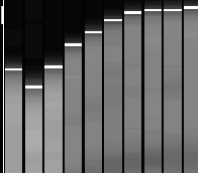
*3.3.3 Experiment 2: Natural End-Expiratory Variability*

We next sought to quantify the effects of natural end-expiratory variability. Twenty new healthy volunteers were recruited. In these subjects, 10 basal and apical images were each acquired with two protocols: 1) during consecutive

Measured End-Expiratory

Diaphragm Positions

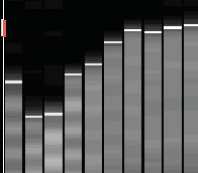
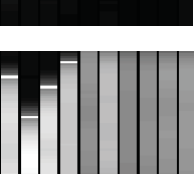
60



Defined Subject-Specific End-Expiratory Positions

Maximum Middle Minimum

50



Exhale

Relative Position (mm)

40

30

20

10

Inhale

0

1 10

Breath-hold Number

**Figure 3.4: Measured end-expiratory diaphragm positions were used to define subject specific maximum, middle, and minimum end-expiratory positions.** The maximum diaphragm position was defined as being closer to the end-expiratory position while the minimum diaphragm position was defined as being closer to the end-inspiratory position.

Torsion Permutations

1 2 3 4 5 6 7 8

For Inter-test

Comparison

9 Repeat 5

Base

Apex

Maximum Maximum Maximum

Maximum Middle Minimum

Middle Middle Middle

Maximum Middle Minimum

Minimum Minimum

Maximum Middle

Minimum

Minimum

Middle

Middle

**Figure 3.5: The nine possible torsion permutations were constructed from three basal and three apical images.** One basal and apical image was acquired for each subject specific end-expiratory position (maximum, middle, and minimum). Image acquisitions were repeated at the middle position to assess inter-test variability (far right).

breath-holds, and 2) during consecutive navigator-gated acquisitions with a single acceptance window location. In each case, the 10 image pairs were used to derive 20 measurements of LV torsion, by combining each basal twist measurement with the two closest apical twist measurements in the temporal sequence. The torsion variability between these protocols was then quantified to compare the differences as a result of consistent (navigator-gated) and inconsistent (breath-hold) end-expiratory positions. Importantly, to monitor the end-expiratory position of the breath-hold acquisitions, the scans were acquired with the respiratory navigator

enabled, but with a wide (*±*50 mm) acceptance window width that never resulted in

the exclusion of acquired image data.

*3.3.4 Statistics*

Statistical analyses were performed using R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). All continuous variables were expressed as mean *±* standard deviation and group means were compared using Student’s t tests. Pearson correlation was used to observe associations between continuous variables.

For experiment 1, the inter-test variability of torsion was quantified using 95% inter-test limits of agreement of the two middle navigator acceptance window scans. To test for an overall difference in variability between inconsistent and consistent end- expiratory positions, the LV torsion permutations from the variable end-expiratory positions were compared to the 95% inter-test limits of agreement using a binomial test to evaluate whether values fell within the 95% limits significantly less than 95% of the time. The root mean squared error (RMSE) was then computed to quantify the differences in variability. Specifically, the RMSE for the consistent end-expiratory position was computed by computing the mean squared error (MSE) of the two middle acceptance window scans and taking the square root. The RMSE for the LV torsion permutations was computed by separately computing the MSE of the permutations with respect to each of the two middle acceptance window scans, averaging the MSEs,

and taking the square root.

For experiment 2, breath-hold and navigator-gated acquisitions were compared by computing the standard deviations of the 20 respective measurements and performing a Student’s t test. Variability in torsion was also quantified using 95% inter-test limits of agreement, which were computed using the standard deviation of the difference between consecutive pairs of torsion measurements. For all statistical tests, significance was defined as p *<* 0.05.

*3.3.5 Theoretical Sample Size Calculation*

To quantify the effects of the differences in torsion measurement variability, we computed theoretical sample sizes required to detect a clinically meaningful change in LV torsion for each experimental condition. Study sample sizes required to detect a 10% relative difference in LV torsion with a power of 90% and a significance level of 0.05 were computed using the standard deviation of the inter-test differences in torsion (*α*) and the equation:

2

*n* = *f* (*α, P* ) *σ*2

*· ·*

*δ*2

(3.1)

where *n* is the sample size per group, *α* is the significance level, *P* is the power, *f*

is the value of the factor for different values of *α* and *P* (*f* = 10.5 for *α* = 0.05 and *P*

= 0.90), and *δ* is the magnitude of the difference to be detected [49]. To determine the improvement in sample size compared to other modalities, sample sizes calculated by this formula were compared to those calculated based on data from previous studies that quantified LV torsion.

**3.4 Results**

For experiment 1, ten healthy volunteers (Age: 22 *±* 6 years, Range: 19*−*38 years,

60% female) and seven patients (Age: 57 *±* 8 years, Range: 45*−*67 years, 43% female)

were enrolled. One healthy volunteer was excluded due to movement during imaging, so data from the remaining nine healthy volunteers are reported. For experiment 2,

20 healthy volunteers (Age: 25 *±* 4 years, Range: 20*−*34 years, 60% female) were

enrolled.

*3.4.1 Inconsistent End-Expiratory Positions*

From experiment 1, the intra-subject range and standard deviation of end-expiratory positions were 10.2 *±* 4.4 mm and 3.3 *±* 1.4 mm, respectively. There was no significant difference in the range or standard deviation of end-expiratory position between healthy and patient groups (p = 0.94 and p = 0.70, respectively; Figure 3.6). From experiment 2, the intra-subject range and standard deviation of end-expiratory positions over 20 breath-holds were 13.9 *±* 10.5 mm and 3.8 *±* 3.1 mm, respectively.

*3.4.2 Torsion*

DENSE images and displacements from a representative subject show the relative twist differences between the base and apex at end-systole (Figure 3.7). Table 3.1 summarizes the LV torsion results for each protocol. From experiment 1, the inter- test limits of agreement at a consistent position were *±*0.6 *◦*/cm, and the binomial test indicated that the variability in LV torsion due to enforced variability in end- expiratory position was significantly higher than the variability at a consistent end- expiratory position (p *<* 0.001). Specifically, the RMSE of LV torsion permutations across end-expiratory positions was 0.56 *±* 0.24 *◦*/cm (range: 0.2*−*1.3 *◦*/cm), while the RMSE from a consistent end-expiratory position was 57% lower (0.24 *±* 0.16 *◦*/cm). Moreover, there was a moderate correlation across subjects between the torsion RMSE and the range of end-expiratory positions (r = 0.50, p = 0.049, Figure 3.8). Finally, the mean LV torsion for consistent end-expiratory positions was not significantly different between the healthy (3.6 *±* 1.2 *◦*/cm) and patient (3.2 *±* 1.3 *◦*/cm) groups

a 25

Range of End-Expiratory Position (mm)

20

15

p = 0.94

b 7

p = 0.70

6

Standard Deviation of

End-Expiratory Position (mm)

5

4

10 3

2

5

1

0

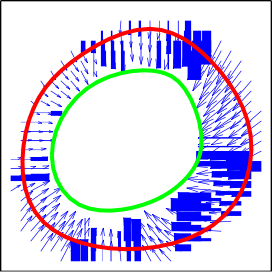
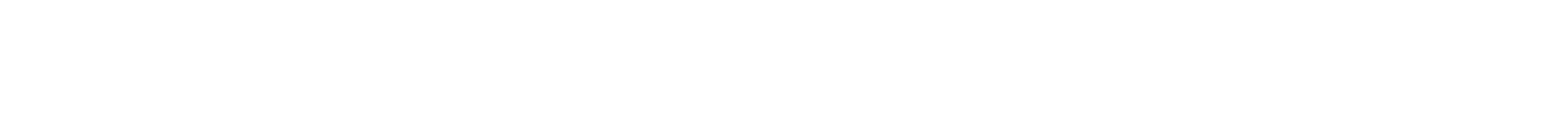
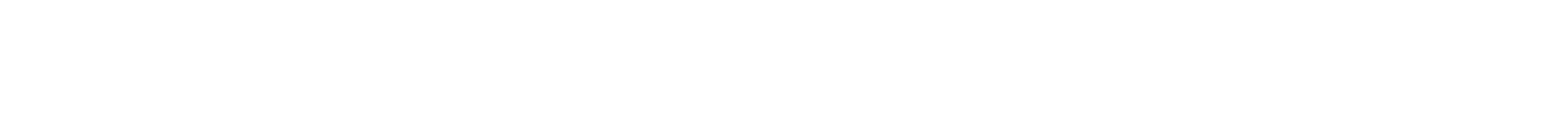
Healthy Patient

0

Healthy Patient

**Figure 3.6: Inconsistent end-expiratory positions across ten consecutive breath holds in patients and healthy controls.** There were no significant differences in either the range (**a**) or standard deviation (**b**) of end-expiratory position between the healthy and patient groups. Solid red lines denote the mean for each group.

Magnitude X-Displacement Y-Displacement 2D Displacements



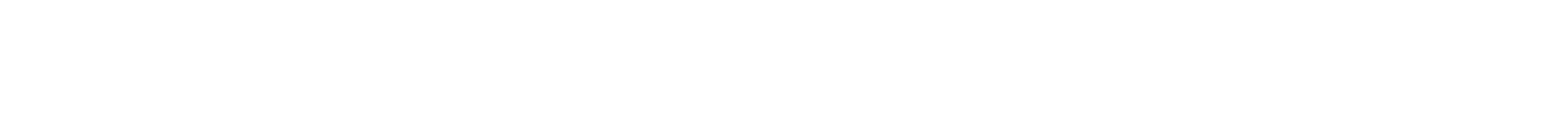
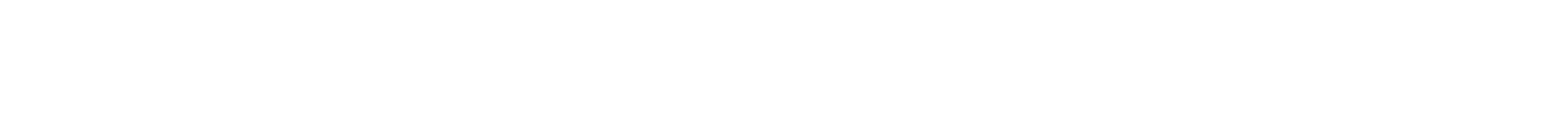
Base



Left Right Up Down



Apex



Left Right Up Down

**Figure 3.7: DENSE images from a representative subject show the relative twist differences between the basal and apical images at end systole.** Twist in the basal region is predominantly in the clockwise direction, while the apex is predominantly counter clockwise.

(p = 0.30).

For experiment 2, consecutive breath-holds yielded a significantly larger standard deviation of LV torsion compared to consecutive navigator scans (0.24 *±*

0.10 *◦*/cm vs 0.18 *±* 0.06 *◦*/cm, p = 0.02). There was a moderate correlation across

subjects between the standard deviation of torsion and the standard deviation of end-expiratory position (r = 0.34, p = 0.03, Figure 3.9). The 95% limits of agreement from the consecutive breath-hold scans and consecutive navigator scans

were *±*0.74 *◦*/cm and *±*0.56 *◦*/cm, respectively.

*3.4.3 Theoretical Sample Sizes*

The theoretical sample sizes required to detect a 10% relative difference in peak torsion (*δ* = 0.34 *◦*/cm) from each experimental protocol are shown in Table 3.2. From both experiments, using a respiratory navigator with DENSE produced similar sample size estimates (*n* = 16 and 15). By comparison, sample sizes based

**Table 3.1: Mean (***±* **standard deviation) of torsion across the volunteers**

**within each experiment.**

**Method (experiment) Torsion (***◦***/cm) p-value**

*Experiment 1\**

Enforced inconsistent positions 3.4 *±* 0.4 0.85

Consistent positions with navigator 3.4 *±* 0.2

*Experiment 2*

Enforced inconsistent positions 3.6 *±* 0.3 0.32

Consistent positions with navigator 3.5 *±* 0.2

\*Reported values are from combined group of healthy and patient volunteers

1.5

RMSE of Torsion (°/cm)

1

Healthy

Patient

r = 0.50

p = 0.049

0.5

0

0 5 10 15 20

Range of End-Expiratory Position (mm)

**Figure 3.8: Variability of torsion due to enforced inconsistent end- expiratory positions versus the subject specific range of end-expiratory position.** There was a moderate positive correlation between RMSE of LV torsion due to inconsistent expiratory positions and the range of end-expiratory position (r

= 0.50, p = 0.049). The dashed gray line illustrates the linear best fit.

0.5

Standard Deviation

of Torsion (°/cm)

0.4

0.3

0.2

0.1

0

Navigated

Breath-hold

r = 0.34

p = 0.03

0 5 10 15

Standard Deviation of

End-Expiratory Position (mm)

**Figure 3.9: Variability of torsion due to naturally inconsistent end- expiratory positions versus the standard deviation of end-expiratory position.** There was a moderate positive correlation between the standard deviation of LV torsion and the standard deviation of end-expiratory position (r = 0.34, p =

0.03). The dashed gray line illustrates the linear best fit.

on measurements with variable end-expiratory positions were up to 313% higher. Additionally, compared to other modalities, using a respiratory navigator with DENSE provided a 80 to 86% reduction in the required sample size compared to CMR tagging [19], CMR feature tracking [43], and 3D speckle tracking echocardiography [44] (Table 3.2).

**3.5 Discussion**

This study explored the effects of inconsistent end-expiratory diaphragm positions on the quantification of LV torsion and how enforcing a consistent end-expiratory position with a respiratory navigator can significantly reduce inter-test variability of measured LV torsion. Our primary findings include 1) using a respiratory navigator with DENSE to enforce a consistent end-expiratory position reduced the variability in measuring torsion by 2257%; 2) this decreased variability reduced the required sample sizes to detect a 10% relative difference in torsion from *n* = 66 to *n* = 16 (from enforced variability to consistent) and *n* = 26 to *n* = 15 (from natural variability to consistent); 3) the variability of LV torsion due to inconsistent end-expiratory

**Table 3.2: Sample sizes required to detect a 10% relative change in LV**

**torsion calculated using data in this and previous studies.**

**Method (experiment) Sample Size (n)**

*Experiment 1*

Enforced inconsistent positions 66

Consistent positions with navigator 16

*Experiment 2*

Enforced inconsistent positions 26

Consistent positions with navigator 15

*Previous Studies*

|  |  |
| --- | --- |
| CMR Tagging [19] | 107 |
| CMR Feature Tracking [43] | 81 |
| 3D Speckle Tracking [44] | 80 |

positions had a modest correlation with the variability in end-expiratory positions, such that greater inconsistency in end-expiratory positions was associated with larger errors in measured LV torsion. Regarding inconsistency in end-expiratory positions,

within each subject, substantial inconsistency existed with a mean range of 10 *±* 4

mm and 14 *±* 10 mm in experiment 1 and 2, respectively, which was similar to that reported previously (7 to 13 mm) [21, 22, 23, 24, 25].

LV torsion is an important indicator of cardiac function because it integrates the three dimensional deformation of the complex myocardial fiber architecture into a single metric [41, 42]. In many disease states, small disruptions in normal cardiac geometryand thus torsionmay precede appreciable changes in global cardiac function. For example, previous studies in mice and canines have reported that changes in torsion precede changes in ejection fraction and volumes in obese animals compared to healthy controls [50, 51]. Previous human studies have reported that LV torsion differs between younger and older populations, and is also reduced in patients with hypertrophic cardiomyopathy, valvular heart disease, previous myocardial infarction, and dilated cardiomyopathy compared to healthy controls [42, 47, 52, 16, 53, 54]. Therefore, accurate and reproducible quantification of LV

torsion may provide a robust, clinically relevant marker of cardiac health and function.

For LV torsion to be a useful clinical measurement, minimizing the magnitudes and sources of measurement error is important. A previous CMR tagging study reported mean torsion values of 3.4 *◦*/cm with inter study 95% limits of agreement

of *±*1.6 *◦*/cm, representing a large percentage of the mean [19]. Previous CMR

feature tracking studies have reported inter-test limits of agreement of *±*0.9 *◦*/cm

[43, 55]. Using DENSE CMR, we observed a similar mean of 3.4 *◦*/cm for all subjects combined in experiment 1 and 3.5 *◦*/cm in experiment 2, and smaller inter-test 95% limits of agreement from the breath hold scans in experiment 2

(*±*0.74 *◦*/cm). However, the observed inter-test 95% limits of agreement were

considerably smaller when using a respiratory navigator (*±*0.6 *◦*/cm and *±*0.56

*◦*/cm for experiments 1 and 2, respectively). An important distinction between the present study and previous studies, apart from CMR sequence differences, is control of the end-expiratory position when quantifying the inter-test variability.

From experiment 1, by comparing the variability of LV torsion inclusive of enforced inconsistent end-expiratory positions (0.56 *±* 0.34 *◦*/cm) to the variability without this

inconsistency (0.24 *±* 0.16 *◦*/cm), we determined that using a respiratory navigator

to ensure a consistent end-expiratory position reduced the variability in measured LV torsion by 57%. In experiment 2, using a respiratory navigator reduced the variability in measured LV torsion by 22% compared to the variability in LV torsion inclusive of naturally inconsistent end-expiratory positions.

In this study, we examined variability in measured LV torsion. A previous CMR study examined the bias in LV twist and circumferential longitudinal (CL) shear angle between different acquisition techniques, including breath holds and free breathing [56]. In agreement with that previous study [56], we did not observe a bias in torsion between breath hold and navigator gated scans (Table 3.1).

To detect a 10% relative difference in peak LV torsion, experiment 1 found that using DENSE with a respiratory navigator required a sample size of only *n* = 16 subjects, which is about 76% lower than the sample size required when using DENSE without a respiratory navigator (*n* = 66). In experiment 2, we found similar results where using DENSE with natural respiratory variability required a sample size of 26 compared to using DENSE with a respiratory navigator (*n* = 15). Using a respiratory navigator with DENSE provided a 80 to 86% reduction in the required sample size compared to CMR tagging [19], CMR feature tracking [43], and 3D speckle tracking echocardiography [44].

These findings have meaningful implications for future CMR based quantification of LV torsion in the clinical and research settings. First, acquisition of LV torsion data using a respiratory navigator should be employed, where feasible, to minimize variability. This approach is not typical in the majority of published papers reporting torsion and may reduce clinical feasibility of such data acquisition; however, the additional effort appears justified by the considerable reduction in variance. If inconsistency in end-expiratory position is not addressed with the data acquisition, then it is important to incorporate effects of inconsistent end-expiratory position into the assessment of the standard error of measurement for LV torsion, which will substantially increase needed sample sizes for research trials or reduce prognostic value for individual subjects.

These results also have important implications for echocardiography. While operators may be able to correct for inconsistency in end-expiratory position by adjusting the position of the probe, it is unlikely that the operator can recreate the exact distance between each short axis image that was measured from the long axis image. Because inconsistent end-expiratory positions is a source of measurement variability in measured LV torsion in CMR, the discrepancy in distances may be a source of substantial variability in measured LV torsion in echocardiography.

We used spiral cine DENSE to investigate our hypothesis that inconsistent end- expiratory positions accounts for a significant portion of the variability in measured torsion and that inter-test reproducibility could be improved by using a respiratory navigator. We chose to use spiral cine DENSE to investigate our hypothesis since it allows for simple quantification of mechanics, has good spatial resolution, has good reproducibility, and includes a respiratory navigator, which allows control of the end- expiratory position during image acquisition [45, 5, 4, 13]. However, our findings should generalize to all other imaging modalities that use short axis images to quantify torsion.

*3.5.1 Limitations and Future Directions*

We examined the effects of variable end-expiratory position on LV torsion in a small patient sample. It may be beneficial to examine these results in a larger, more heterogeneous patient sample to determine whether specific diseases affect the results more than others, especially conditions that affect a patient’s ability to repeatedly hold his or her breath reproducibly (for example, pulmonary diseases).

Due to the lengthy duration of DENSE breath holds ( 20 seconds) and their limitations in breath-holding ability, the breath-hold acquisition protocol was not performed in patients. Based on these factors, we expect that patients would demonstrate higher variability in LV torsion with the breath-hold measures compared to the healthy volunteers we studied. Hence, the potential reduction in mean variability when using the respiratory navigator may in fact be higher than the 22% we report from the healthy volunteers in experiment 2. Nevertheless, the reduction in LV torsion variability patients will achieve by using a respiratory navigator will likely fall between the study’s reported values of 22 and 57%.

**3.6 Conclusion**

Using a respiratory navigator to enforce a consistent end-expiratory position during image acquisition can reduce the variability in measured LV torsion by

22*−*57%. Accounting for inconsistent end-expiratory positions results in favorable

inter-test variability and reduces required sample sizes by 80 to 86% compared to previous studies. Future efforts to measure LV torsion should use a respiratory navigator or similar form of consistent respiratory compensation.

**CHAPTER 4**

**OPTIMAL RESPIRATORY NAVIGATOR CONFIGURATION**

*Adapted from Hamlet SM, Haggerty CM, Suever JD, Wehner GJ, Andres KN, Powell DK, Zhong X, Fornwalt BK. Optimal Configuration of Respiratory*

*Navigator Gating for the Quantification of Left Ventricular Strain Using Spiral Cine Displacement Encoding with Stimulated Echoes (DENSE) MRI. Journal of Magnetic Resonance Imaging. 2017. 45(3):796-794*

The purpose of this work was to determine the optimal respiratory navigator gating configuration for the quantification of left ventricular strain using spiral cine displacement encoding with stimulating echoes (DENSE) MRI. In this chapter, we detail the different respiratory navigator configurations, their advantages and disadvantages, and the experimental protocol. This study identifies the optimal respiratory navigator configuration in adults and children compared to the

”gold-standard” breath-hold acquisition.

**4.1 Synopsis**

**Purpose:** To determine the optimal respiratory navigator gating configuration for the quantification of left ventricular strain using spiral cine displacement encoding with stimulated echoes (DENSE) MRI.

**Methods:** Two-dimensional spiral cine DENSE was performed on a 3 Tesla MRI using two single-navigator configurations (retrospective, prospective) and a combined dual-navigator configuration in 10 healthy adults and 20 healthy children. The adults also underwent breathhold DENSE as a reference standard for comparisons. Peak left ventricular strains, signal-to-noise ratio (SNR), and navigator efficiency were compared. Subjects also underwent dual-navigator gating with and without visual feedback to determine the effect on navigator efficiency.

**Results:** There were no differences in circumferential, radial, and longitudinal strains between navigator-gated and breath- hold DENSE (P = 0.09—0.95) (as confidence intervals, retrospective: [-1.0%–1.1%], [-7.4%–2.0%], [-1.0%1.2%]; prospective: [-0.6%–2.7%], [-2.8%–8.3%], [-0.3%–2.9%]; dual: [-1.6%–0.5%], [-8.3%–3.2%], [-0.8%–1.9%], respectively). The dual configuration maintained SNR compared with breathhold acquisitions (16 versus 18, P = 0.06). SNR for the prospective configuration was lower than for the dual navigator in adults (P = 0.004) and children (P *<* 0.001). Navigator efficiency was higher (P *<* 0.001) for both retrospective (54%) and prospective (56%) configurations compared with the dual configuration (35%). Visual feedback improved the dual configuration navigator efficiency to 55% (P *<* 0.001).

**Conclusion:** When quantifying left ventricular strains using spiral cine DENSE MRI, a dual navigator configuration results in the highest SNR in adults and children. In adults, a retrospective configuration has good navigator efficiency without a substantial drop in SNR. Prospective gating should be avoided because it has the lowest SNR. Visual feedback represents an effective option to maintain navigator efficiency while using a dual navigator configuration.

**Keywords:** Respiratory Navigator, Breath-holds, DENSE, Strain, Signal-to-Noise

Ratio, Navigator Efficiency

**4.2 Introduction**

Magnetic resonance (MR) can be used to non-invasively assess cardiac function. Displacement encoding with stimulated echoes (DENSE) is an advanced cardiac MR imaging technique that directly measures tissue displacements and can be used to quantify cardiac mechanics, such as myocardial strains and torsion [4, 13]. When combined with clinical risk factors, these measures of cardiac mechanics have been shown to be better predictors of mortality than traditional measures of cardiac function, such as ejection fraction [3].

Compensation for respiratory motion is an important consideration for all cardiac MR techniques, particularly quantitative imaging sequences like spiral cine DENSE. DENSE acquisitions are generally performed using end-expiratory

breath-holds (*∼*15-20 seconds in duration) [32, 31, 57, 45, 58, 36, 59]; however, this

approach is constrained by the patient’s ability to breath-hold, which is limited in young subjects and many stages of advanced heart disease. Furthermore, short acquisitions preclude the ability to capture more robust data, such as three-dimensional (3D) DENSE [45, 60, 61], or high resolution imaging [62].

As with many other cardiac MR sequences, a respiratory navigator has been used to overcome this time limitation by allowing the subject to breathe freely but restricting data acquisition based on the position of the diaphragm within a prescribed ’acceptance’ window [45]. However, unlike some other MR sequences, the navigator echo in the DENSE sequence cannot occur at the beginning of the cardiac cycle, since this would lead to interference with displacement encoding. Instead, the navigator echo must occur at the end of the cardiac cycle, immediately after data acquisition. This creates several options for how the navigator can then be used to either accept or reject the acquired DENSE data (Figure 4.1). For example, a single echo can be used retrospectively or prospectively to define acceptance of DENSE data from the current or preceding cardiac cycle, respectively. Alternatively, a

dual-navigator configuration can be used, which requires an echo from the current and preceding cardiac cycle to define acceptance of DENSE data (Figure 4.1). Each configuration has distinct advantages and disadvantages. For example, compared to the single navigator configurations, the dual-navigator configuration has more rigorous criteria for correctly accepting data (Figure 4.2). However, these strict criteria likely lead to worse navigator efficiency compared to the single navigator configurations (Figure 4.2).

Previous studies using navigator-gated DENSE have reported using a prospective single navigator configuration [45, 61]. However, there has been no formal comparison of the available navigator configurations. Moreover, the accuracy of derived cardiac mechanics and overall image quality for these navigator configurations compared with breath-hold acquisitions as a reference standard are largely unknown. The purpose of this study was to determine the optimal configuration of respiratory navigator gating for the quantification of left ventricular strain using spiral cine DENSE MRI.

**4.3 Methods**

*4.3.1 Subjects*

Ten healthy adults and 20 healthy children with no known history of cardiovascular disease or chronic illnesses and a normal 12-lead electrocardiogram were prospectively enrolled. The protocol was approved by the local Institutional Review Board and all subjects provided informed consent (or assent/parental consent, as appropriate).

*4.3.2 Image Acquisition*

Image acquisition was performed on a 3T Siemens Tim Trio (Siemens Healthcare, Erlangen, Germany) with a 6-element chest coil and a 24-element spine coil. 2D spiral cine DENSE [45, 46] in mid-ventricular short-axis and four-chamber long-axis orientations were separately acquired using breath-holds and retrospective, prospective, and dual navigator gating. Due to the lengthy breath-hold duration

Navigator Gating Configurations

|  |  |  |
| --- | --- | --- |
|  | Navigator Pulse |  |
|  |
| DENSE Imaging |
|  |
| Gates R-R Int. N |

Data are acquired if

R-R

Interval N-1

Pro.

R-R

Interval N

the diaphragm is within the acceptance window:

(a) Prospective

Pro.

DENSE Data Acquisition

Before

Data Acquisition

(b) Retrospective

Retro.

DENSE Data Acquisition

Retro.

After

Data Acquisition

(c) Dual

DENSE Data Acquisition

Retro.

Before and After

Data Acquisition

**Figure 4.1: Different navigator gating configurations used to acquire DENSE image data.** The single navigator configurations: (**A**) prospective and (**B**) retrospective; and the (**C**) dual navigator configuration. The red outlines and arrows indicate which navigator pulse(s) is/are gating the DENSE data acquisition.

Pro.

Prospective

Correctly Discarded

Incorrectly Accepted

Correctly Discarded

Correctly Accepted

Retrospective Incorrectly Accepted

Correctly Discarded

Incorrectly Accepted

Correctly Accepted

Dual

Correctly Discarded

Correctly Discarded

Correctly Discarded

Correctly Accepted

DENSE Data Acquisition

DENSE Data Acquisition

DENSE Data Acquisition

DENSE Data Acquisition

Acceptance Window

Respiratory Signal

**Figure 4.2: Theoretical example to demonstrate the disadvantages of single- and dual-navigator gating configurations.** The red colored text identifies the incorrectly accepted DENSE data from single-navigator gating configurations (i.e. the diaphragm is not within the acceptance window for the entirety of DENSE data acquisition, but the data are still accepted). The number of Accepted/Discarded data in the example above illustrate how a dual navigator gating configuration will discard more data compared to single navigator gating configurations (retrospective and prospective) and lead to lower navigator efficiency. The red ’x’ or green ’o’ represents the detected diaphragm location being outside or inside the acceptance window, respectively.

(*∼*20 seconds), breath-hold acquisitions were not performed in children. The order of the navigator gating configurations was randomized. Prospective ECG gating was used and the number of cardiac phases was selected to allow 100-150 ms at the end of the cardiac cycle for heart rate variability. Acquisition parameters for all scans were: spiral type: uniform density, interleaves = 6, interleaves per beat = 2, FOV =

360x360 mm2, pixel spacing = 2.8x2.8 mm2, slice thickness = 8 mm, TE = 1.1 ms, TR = 17 ms, variable flip angle = 20*◦* [46, 63], displacement encoding = 0.06 cyc/mm [6], through-plane dephasing = 0.08 cyc/mm [31] CSPAMM echo suppression [32], and view sharing. The temporal resolution was 34 ms, however sliding window view sharing yielded a 17 ms temporal resolution between reconstructed cardiac frames. Based on the DENSE parameters, acquisition duration for each orientation was 20 heartbeats.

The respiratory navigator was placed over the dome of the liver. Subjects were

asked to breathe comfortably and a scout navigator was used to track the diaphragm. The navigator acceptance window was placed so that the maximum acceptance window position was located 1-2 millimeters above the subject’s

maximum expiration position. A navigator acceptance window of *±*3 mm (total

range of 7 mm) was used for all navigator gated scans. Navigator efficiency was measured as the number of cardiac cycles from which data were acquired and accepted over the total number of cardiac cycles required to complete a scan.

*4.3.3 Navigator Feedback*

Because the dual-navigator configuration was expected to decrease navigator efficiency, we developed and tested a feedback system, which allowed the subject to view their diaphragm position in real-time during image acquisition. The goal was to compensate for reduced navigator efficiency in order to preserve the clinical feasibility of DENSE imaging using a dual-navigator configuration.

The feedback system consisted of an angled mirror placed above the patient’s head so that an image of the diaphragm location was viewable on a screen located at the back of the scanner bore. The image of the diaphragm location (respiratory navigator display) was projected from the scanner console’s video feed onto the screen with an MRI-compatible projector. After all other scans were completed, subjects used this feedback system, with the dual-navigator gating configuration, to acquire the same short-axis and long-axis images.

This feedback system was also used prior to the breath-hold scan to ensure a consistent end-expiratory diaphragm location between the navigator-gated acquisitions and the breath-hold acquisitions. With instruction, the subject exhaled and breath-held in the acceptance window, at which point the navigated scan was halted and the breath-hold acquisition was immediately performed. Breath-hold acquisitions were always performed after the navigator-gated acquisitions that did not involve navigator feedback in order to minimize the potential effect of navigator

feedback on respiratory patterns.

*4.3.4 DENSE Post-Processing*

All DENSE images were analyzed using custom, open-source MATLAB (The Mathworks Inc, Natick, MA) software, *DENSEanalysis* [34]. For each set of DENSE images, endocardial and epicardial boundaries were drawn on the magnitude image from an end-diastolic and end-systolic frame. A simplified analysis technique was used to reconstruct the motion field [35]. The displacement-encoded phase images were unwrapped using a path-following algorithm with manual selection of seed points. The resulting Lagrangian displacements underwent spatial smoothing and temporal fitting as previously described [36].

Segmental two-dimensional Lagrangian strains were computed over the cardiac cycle for 6 segments in the short-axis images (radial and circumferential strain) and from the long-axis images (longitudinal strain). Cardiac segments were defined using the American Heart Association 17-segment model. Average peak strains were computed by averaging the strain curves of all the myocardial segments together and finding the peak of this average strain curve. When computing peak longitudinal strain, pixels within 10% of left ventricular longitudinal length from the most basal and apical regions were excluded in order to exclude the increased noise which is typically observed in the strain curves in those regions. Thickening was defined by convention as positive strain, whereas shortening was defined as negative.

*4.3.5 Analysis*

Mean modified coefficient of variation (CoV) [6, 5, 46] was used to measure agreement in strain between different navigator configurations and breath-holds. The calculation of the CoV is shown below where *N* is the number of subjects and *x*1 and *x*2 are the strain measurements.

*C oV* = *i*=1[*St.Dev*(*x*1[*i*]*, x*2[*i*])]*/N*

Σ *N*

(4.1)

*N*

*|*Σ

*i*=1

[(*x*1[*i*] + *x*2[*i*])*/*2]*/N |*

Consistent with previous studies reporting CoVs [5, 64, 65, 55, 43], results less than or equal to 20% were considered acceptable.

To compare image quality, signal-to-noise ratio (SNR) was computed using the DENSE magnitude images at end-systole. SNR was quantified from the average myocardial signal and the standard deviation of the noise within an area free from tissue or imaging artifacts [6, 46, 66]. Because the MR signal has a Rician distribution, corrections were applied in order to calculate the true SNR [67]. The measured

standard deviation, *σM* , was used to compute the true standard deviation, *σ*, by

2

*σ* =

4 *− π*

*∗ σM ≈* 1*.*526 *∗ σM* (4.2)

The measured myocardial signal, *M* , was used to compute the true myocardial signal, *S*, by

*S* = *√M* 2 *− σ*2 (4.3) SNR was defined as the ratio of the true myocardial signal (*S*) to the true standard

deviation (*σ*).

*4.3.6 Comparison of Acquisition Configurations*

We compared peak global and segmental strains (circumferential, radial, and longitudinal) and SNR of the end-systolic DENSE magnitude images between each acquisition technique (breath-hold and navigator gating) in adults. Bland-Altman analyses [38], CoV [5], and 95% confidence intervals (CI) were used to measure agreement in strain between the separate navigator configurations and breath-holds. A paired Student’s t-test was used to compare strains between navigator

configurations and breath-holds. We also compared SNR and navigator efficiency between all navigator configurations (dual, retrospective, and prospective) in adults and children using a one-way repeated measures ANOVA with post-hoc analyses

and Bonferroni correction. All data are presented as mean *±* one standard

deviation. Significance was defined as p *<* 0.05.

**4.4 Results**

Ten healthy adults (Age: 23 *±* 3 years, 40% female) and 20 healthy children (Age:

13 *±* 3 years, 45% female) were enrolled in the study. DENSE data were successfully acquired in all subjects except for one child who could not complete the study protocol

due to an erratic respiratory pattern.

*4.4.1 Average Peak Strains*

Average peak left ventricular strains are shown in Table 4.1. There were no significant mean differences in circumferential, radial, and longitudinal strain between the dual, retrospective, and prospective navigator configurations and breath-holds in adults (Figure 4.3). Compared to breath-holds, all navigator configurations had a CoV of less than 20% for circumferential, radial, and longitudinal strain in adults (Figure 4.3). The differences in strain are listed as confidence intervals in Table 4.2. Peak segmental left ventricular strains are shown in Table B.1 in Appendix A). There were no significant differences in segmental strain between the navigator configurations and breath-holds except for radial strain from the prospective configuration (p = 0.002, Table B.2). Compared to breath-holds, all navigator configurations had CoVs of less than 20% except for radial segmental strain (19-28%) (Table B.2).

**Table 4.1: Average strains for different acquisition techniques.**

**Circumferential Strain (%)**

**Mean** *±* **Std. Dev.**

**Adults Children**

Breath-hold -17 *±* 2 – Retrospective -18 *±* 2 -19 *±* 2

Prospective -17 *±* 3 -18 *±* 2

Dual -18 *±* 3 -20 *±* 2

**Radial Strain (%)**

|  |  |  |
| --- | --- | --- |
| Breath-hold Retrospective Prospective Dual | 30 *±* 10  26 *±* 9  31 *±* 7  27 *±* 9 | –  30 *±* 9  26 *±* 12  27 *±* 12 |
| **Longitudinal Strain (%)** | | |
| Breath-hold  Retrospective Prospective Dual | -14 *±* 2  -14 *±* 2  -13 *±* 2  -14 *±* 2 | –  -14 *±* 2  -14 *±* 2  -14 *±* 2 |

**Table 4.2: CI Results for Differences in Strain Between Navigator Gating and Breathhold DENSE.**

**Circumferential Strain (%)**

**95% LoA p-value**

Retrospective–Breath-hold [-1.0–1.1] 0.95

Prospective–Breath-hold [-0.6–2.7] 0.17

Dual–Breath-hold [-1.6-0.5] 0.29

**Radial Strain (%)**

|  |  |  |
| --- | --- | --- |
| Retrospective–Breath-hold | [-7.4–2.0] | 0.23 |
| Prospective–Breath-hold | [-2.8–8.3] | 0.29 |
| Dual–Breath-hold | [-8.3-3.2] | 0.34 |
| **Longitudinal Strain (%)** | | |
| Retrospective–Breath-hold | [-1.0-2.0] | 0.85 |
| Prospective–Breath-hold | [-0.3-2.9] | 0.09 |
| Dual–Breath-hold | [-0.8–1.9] | 0.38 |

Retro vs Breath-hold Pro vs Breath-hold

Dual vs Breath-hold

Ecc

Ecc Retro − BH (%)

Mean CoV = 5%

6

4

2

0

−2

−4

p = 0.95

−6

2.9

0.0

−2.9

Mean CoV = 8%

6

|  |
| --- |
|  |
| 5.6  1.1 |
| −3.4 |
| p = 0.17 |

4

Ecc Pro − BH (%)

2

0

−2

−4

−6

Mean CoV = 6%

6

|  |
| --- |
| 2.4 |
| −0.5 |
| −3.4 |
| p = 0.29 |

4

Ecc Dual − BH (%)

2

0

−2

−4

−6

−22 −20 −18 −16 −14 −12

Mean (%)

−22 −20 −18 −16 −14 −12

Mean (%)

−22 −20 −18 −16 −14

Mean (%)

Mean CoV = 15%

20

|  |
| --- |
| p = 0.23  10.3 |
| −2.7 |
| −15.7 |
|  |

10

Err Retro − BH (%)

Mean CoV = 14%

20

|  |
| --- |
|  |
| p = 0.29 18.0  2.8 |
| −12.5 |
|  |

10

Mean CoV = 17%

20

|  |
| --- |
| p = 0.34 13.3 |
| −2.6 |
| −18.4 |
|  |

10

Err 0 0 0

Err Pro − BH (%)

Err Dual − BH (%)

−10

−10

−10

−20

10 20 30 40 50

Mean (%)

−20

10 20 30 40 50

Mean (%)

−20

10 20 30 40 50

Mean (%)

6

|  |
| --- |
| 3.2 |
| 0.1 |
| −3.0 |
| p = 0.85 |

4

Ell Retro − BH (%)

2

Ell

0

−2

−4

−6

Mean CoV = 7%

Mean CoV = 11%

6

4

Ell Pro − BH (%)

2

0

−2

−4

p = 0.09

−6

6

5.7

4

Ell Dual − BH (%)

1.3 2

0

−3.0 −2

−4

−6

Mean CoV = 8%

−18 −16 −14 −12 −10

Mean (%)

−16 −14 −12 −10

Mean (%)

−16 −14 −12

Mean (%)

|  |
| --- |
| 4.2 |
| 0.5 |
| −3.1 |
| p = 0.38 |

**Figure 4.3: Bland-Altman plots of average peak circumferential (Ecc), radial (Err), and longitudinal (Ell) strains for retrospective, prospective, and dual navigator gating vs breath-hold.**

**Table 4.3: Signal-to-noise ratios for different navigator gating configurations in adults and children.**

**Adults p-value Children p-value**

Breath-hold 18 *±* 8

Retrospective 15 *±* 6\**†*

*<* 0.001

–

22 *±* 6*‡*

*<* 0.001

Prospective 13 *±* 5\* 20 *±* 8*‡*

Dual 16 *±* 7 27 *±* 9

\* p *<* 0.05 vs. breath-hold; *†* p *<* 0.05 vs. prospective; *‡* p *<* 0.05 vs. dual

*4.4.2 Signal-to-Noise Ratio*

In adults, single navigator configurations had a 17-28% reduction in SNR compared to breath-hold DENSE (Table 4.3). There was no difference in SNR between the dual navigator configuration and breath-hold DENSE (p = 0.06). Among navigator configurations, dual and retrospective navigator configurations were comparable and both had better SNR (23% and 15%, respectively) compared to the prospective configuration (p = 0.02, p = 0.004, respectively).

In children, SNR also differed based on navigator gating configuration (Table 4.3). The dual navigator configuration had the highest SNR compared to the retrospective (23% higher, p *<* 0.001) and prospective (35% higher, p *<* 0.001) configurations. There was no difference in SNR between the retrospective and prospective navigator configurations (p = 0.15).

*4.4.3 Navigator Efficiency*

For adults and children combined, there were significant differences in navigator efficiency between navigator configurations (p *<* 0.001, Table 4.4). The retrospective and prospective navigator configurations had higher navigator efficiencies than the dual navigator configuration by an average of 54% (p *<* 0.001) and 60% (p *<* 0.001), respectively. Using visual feedback with the dual navigator configuration improved navigator efficiency by 57% (p *<* 0.001) compared to the

**Table 4.4: Navigator efficiencies for different navigator gating configurations in adults and children.**

**Pooled p-value Adults Children**

Retrospective 54 *±* 15\* Prospective 56 *±* 15\*

*<* 0.001

48 *±* 15\* 57 *±* 16\*

52 *±* 17\* 58 *±* 14\*

Dual 35 *±* 13 31 *±* 16 37 *±* 11

Dual Feedback 55 *±* 16\* 67 *±* 11\* 48 *±* 15\*

\* p *<* 0.05 vs. dual (without feedback)

dual configuration without feedback and resulted in comparable efficiency to the single navigator configurations. The scan times mirrored the navigator efficiency results. For example, scan times for adults were, on average, 64, 37, 37, and 25 seconds for the dual, retrospective, prospective configurations, and the dual navigator configuration with feedback, respectively.

**4.5 Discussion**

The use of respiratory navigated acquisitions for spiral cine DENSE extends the potential utility of the technique by removing restrictions on patient breath-holding abilities and allowing for high resolution [62] and/or three dimensional [45, 60] data collection. While previous studies have used a respiratory navigator with DENSE, the optimal configuration for gating and how it might differ among subjects has been largely unexplored. This study addressed these knowledge gaps by showing that: 1) left ventricular peak strains were not different between breath-held and navigator- gated DENSE acquisitions; 2) SNR was reduced with single navigator configurations, but not the dual configuration, compared to breath-held acquisitions; 3) the SNR benefit of the dual navigator configuration was offset by reduced navigator efficiency compared to single navigator configurations, but visual navigator feedback maintained clinically acceptable efficiencies for the dual navigator acquisition. The following paragraphs explore each of these findings in greater detail.

There were no significant mean differences and good paired agreement of all

peak strains between retrospective, prospective, and dual navigator configurations and breath-holds in adults. This finding agrees with the prior work by Zhong et al., which compared segmental strains from navigator-gated 3D DENSE to breath-hold

2D DENSE [45] and similarly reported clinically acceptable agreement. Our study extends this work by demonstrating that the agreement exists not only for prospective navigator-gating used by Zhong et al., but for retrospective and dual navigator-gating configurations as well. Demonstrating this agreement of strain valuesa primary endpoint for most DENSE acquisitionshas pragmatic value by ensuring that data from acquisitions with differing respiratory compensation can be readily compared.

Our results demonstrate that using a single navigator configuration resulted in significantly lower SNR compared to breath-hold DENSE acquisitions. While this result was only demonstrated in adults because of the prohibitively long breath-hold duration in children, it is reasonable to assume that a similar trend holds in children as well. Among the navigator configurations, the dual configurations provided the best SNR as it was superior to prospective navigator gating in both adults and children, had better SNR than retrospective gating in children, and resulted in comparable SNR to breath-hold DENSE.

Differences in SNR among the different acquisitions are likely attributable to heart rate and respiratory variability. The breath-hold acquisitions had the shortest acquisition time, with presumably less physiologic variability. Also, the dual navigator configuration had the most stringent acceptance criteria, which likely minimized the effects of respiratory variability during acquisition compared to the other configurations. This reasoning is supported by previous studies, which have reported associations between consistent diaphragm position during navigator-gated acquisitions and improved SNR [68, 69]. In both adults and children, the prospective navigator configuration had the lowest SNR of all navigator

configurations. The observed difference in SNR between the single navigator configurations was perhaps unexpected given the theoretical similarities in their design and function. However, these differences are similarly attributable to the effects of variability: for the retrospective navigator, the interval between the R wave and the navigator echo is fixed, whereas heart rate changes during the scan will affect the interval between the navigator echo and the succeeding R wave in prospective gating, increasing the likelihood of respiratory variability during that interval. Based on these findings, the use of prospective navigator gating for DENSE should be avoided.

Notably, a previous study compared SNR of a 2D steady-state free precession sequence between dual navigator-gated and breath-hold acquisitions and found that end-systolic myocardial SNR for breath-hold acquisitions was 23% lower than the dual navigator configuration in adults [70]. This finding contrasts with our data in which the dual navigator configuration was statistically comparable to breath-hold. However, the previous study had substantially different imaging parameters between their dual navigator-gated acquisition and the breath-hold acquisition, which likely accounted for the observed SNR differences [70].

Although the purpose of this study was to determine the optimal navigator gating strategy, it is worth noting that SNR was higher for children than it was for adults. The difference in SNR between adults and children is likely related to the smaller body habitus of children, which results in a shorter distance between the MRI coils and the heart. Moreover, adults likely have more adipose tissue, which could also lead to lower SNR. Ultimately, these SNR differences may lead to differences in inter-test reproducibility between adults and children.

As expected, single navigator gating configurations resulted in better navigator efficiency compared to dual navigator gating, due to the additional acceptance criteria constraints of the dual navigator. Simply put, more data are discarded with dual

navigator gating, leading to prolonged scan time. Previous studies using a single- navigator configuration with the same size acceptance window (*±*3 mm) reported navigator gating efficiencies ranging from 20 to 48% [45, 68, 71]. Compared to these

studies, we observed slightly better single-navigator efficiencies of 48 to 52% in adults and 57 to 58% in children. The dual navigator efficiency was comparable to results from previous studies [70].

To potentially offset this reduced efficiency, we evaluated the effect of providing the subject with visual feedback of the diaphragm position, which has been shown to considerably improve navigator efficiency compared to traditional free-breathing acquisitions [68]. We found that using visual feedback during dual navigator gated acquisitions improved navigator efficiency compared to the dual configuration without feedback and resulted in comparable efficiency to the single navigator configurations. The improvement with feedback was not uniform across adults and children (i.e., the improvement in kids was not as substantial), perhaps reflecting the superior ability of the adults to hold their breath within the acceptance window. Alternatively, the difference may be indicative of the non-intuitive nature of the respiratory navigator display and the differential abilities of adults and kids to quickly learn and use it. Efforts are ongoing to instead transform this image to a more kid-friendly video game design to improve usability [30].

The increased scan time associated with the dual navigator configuration presents an obvious trade-off with improved SNR for its utility in a clinical setting where time is a critical consideration. In adults, given the minimal difference in SNR between the dual and retrospective navigator configurations, the substantial drop in efficiency with the dual navigator may not be justified. In children, however, the SNR benefit with dual navigator gating is more substantial and warrants consideration to ensure high quality data. Hence the demonstrated improvement in navigator efficiency by providing the subject with visual feedback is an important

finding because it provides one option for compromise: achieving improved SNR while approximately maintaining scan time compared to other navigator configurations.

This study was performed using 2D DENSE. However, given the similarity in the fundamental sequence designs of 2D and 3D DENSE, the results are applicable to

3D DENSE acquisitions as well. In fact, given the longer time generally required for 3D data acquisition, respiratory compensation/navigation is essential, so these results are highly relevant. Specifically, our navigator efficiency findings agree with reported efficiencies from a previous study using 3D DENSE [45]. Also, while absolute magnitudes of SNR may differ with more data acquired, there is no reason to suspect that the relative differences in SNR would change between different navigator gating strategies when applying these results to 3D DENSE.

A limitation of this study is the potentially limited power for detecting small strain differences between navigator configurations and breath-hold DENSE. However, our study had 80% power to detect a difference of 1.5% between the retrospective navigator configuration and breath-holds. This 1.5% difference is smaller than the typical inter-test limits of agreement of circumferential strain [6]. Moreover, even if the strains from the prospective navigator configuration, which had the worst agreement, are in fact different from the breath-hold technique, the conclusions of the study would not change as the prospective navigator configuration was separately found to be sub-optimal based on SNR.

Another limitation was the lack of breath-hold data for the pediatric subjects. The DENSE acquisition required 20 heartbeats. The required breath-hold time was further extended by the use of a navigator-gated pre-scan to ensure that breath-holds were performed at the same diaphragm position as the navigator-gated scans. This duration was viewed to be prohibitively long for pediatric subjects, and so no breath- hold DENSE data were acquired in these cases. The equivalence of DENSE-derived

strains between breath-hold and navigator sequences was demonstrated in adults. Since children did not undergo breath-hold DENSE, we must caution future studies regarding these strain results as they apply to children. However, since the relative SNR and navigator efficiency results from navigator gating were similar to those in adults, we would expect potential differences to be small. Furthermore, the primary objective of the study was to identify optimal navigator configurations for DENSE, so the lack of breath-hold data in children is a minor limitation.

A third limitation of this study is the lack of assessment of clinical patients. Cardiac patients, who routinely undergo MR imaging and who may have limited ability to hold their breath, may not be able to perform the lengthy breath-hold scan and may not achieve as high navigator efficiency when performing a dual navigator scan with feedback. However, since this population is more likely to undergo DENSE MR imaging than this study’s volunteer subjects, it would be beneficial to determine whether the results remain the same. For example, it may be important to use dual navigator gating, even at the expense of navigator efficiency, to achieve higher SNR, since SNR is commonly lower in the clinical patient population compared to healthy volunteers.

In conclusion, for spiral cine DENSE acquisitions, respiratory navigator gating and breath-hold acquisitions yield comparable values of left ventricular peak strains. However, differences in signal-to-noise ratios and navigator efficiencies were observed among the different navigator gating configurations, which warrant consideration in clinical and research protocol design. In adult subjects, the dual navigator configuration produced the best SNR, although only slightly better than the single retrospective navigator, which produced acceptable SNR and therefore may be used to maintain good efficiency. For children, the benefit of a dual navigator configuration for improved SNR was even more apparent, but resulted in a considerable drop in scan efficiency. The prospective navigator resulted in the

poorest SNR and should be avoided. The use of visual navigator feedback represents an effective option to maintain navigator efficiency while using the dual navigator in children (and adults).

**CHAPTER 5**

**INTERACTIVE FEEDBACK GAME DESIGNED TO IMPROVE NAVIGATOR EFFICIENCY**

*Adapted from Hamlet SM, Haggerty CM, Suever JD, Wehner GJ, Grabau JD, Andres KN, Vandsburger MH, Powell DK, Sorrell VL, Fornwalt BK. An interactive videogame designed to improve respiratory navigator efficiency in children undergoing cardiovascular magnetic resonance. Journal of Magnetic Resonance Imaging. 2016. 18:54*

**5.1 Synopsis**

**Background:** Advanced cardiovascular magnetic resonance (CMR) acquisitions often require long scan durations that necessitate respiratory navigator gating. The tradeoff of navigator gating is reduced scan efficiency, particularly when the patient’s breathing patterns are inconsistent, as is commonly seen in children. We hypothesized that engaging pediatric participants with a navigator-controlled videogame to help control breathing patterns would improve navigator efficiency and maintain image quality.

**Methods:** We developed custom software that processed the Siemens respiratory navigator image in real-time during CMR and represented diaphragm position using a cartoon avatar, which was projected to the participant in the scanner as visual feedback. The game incentivized children to breathe such that the avatar was

positioned within the navigator acceptance window (*±*3 mm) throughout image

acquisition. Using a 3T Siemens Tim Trio, 50 children (Age: 14 *±* 3 years, 48%

female) with no significant past medical history underwent a respiratory navigator-gated 2D spiral cine displacement encoding with stimulated echoes (DENSE) CMR acquisition first with no feedback (NF) and then with the feedback

game (FG). Thirty of the 50 children were randomized to undergo extensive off-scanner training with the FG using a MRI simulator, or no off-scanner training. Navigator efficiency, signal-to-noise ratio (SNR), and global left-ventricular strains were determined for each participant and compared.

**Results:** Using the FG improved average navigator efficiency from 33 *±* 15 to 58 *±*

13% (p *<* 0.001) and improved SNR by 5% (p = 0.01) compared to acquisitions with NF. There was no difference in navigator efficiency (p = 0.90) or SNR (p = 0.77) between untrained and trained participants for FG acquisitions. Circumferential and radial strains derived from FG acquisitions were slightly reduced compared to NF

acquisitions (16 *±* 2% vs 17 *±* 2%, p *<* 0.001; 40 *±* 10% vs 44 *±* 11%, p = 0.005,

respectively). There were no differences in longitudinal strain (p = 0.38). **Conclusion:** Use of a respiratory navigator feedback game during navigator-gated CMR improved navigator efficiency in children from 33 to 58%. This improved efficiency was associated with a 5% increase in SNR for spiral cine DENSE. Extensive off-scanner training was not required to achieve the improvement in navigator efficiency.

**Keywords:** Pediatrics, Respiratory navigator, Navigator efficiency, Image quality, Cardiovascular magnetic resonance

**5.2 Background**

Cardiovascular magnetic resonance (CMR) can be used to non-invasively assess heart function. In the clinical setting, CMR techniques play an important role in the diagnosis and monitoring of the complex anatomy and physiology of congenital and acquired heart diseases. Moreover, there is a considerable body of pre-clinical research devoted to the development and evaluation of new, advanced imaging techniques, such as 3D displacement encoding with stimulated echoes (DENSE) [45], 3D steady state free precession [72], and 4D flow imaging [73]. These new techniques have demonstrated ability in distinguishing normal and pathological tissue deformation and blood flow and may become beneficial tools in the diagnosis and management of heart disease. Many of these clinical and pre-clinical techniques require scan durations that exceed patients’ ability to hold their breath.

End-expiratory breath-holds are used by many CMR sequences in order to minimize respiratory-motion artifacts. However, requiring subjects to hold their breath introduces significant limitations on the duration of data acquisition or the quality of the acquired images, particularly for young children or patients with advanced disease. A common alternative is respiratory navigator gating, which works by measuring the diaphragm position during normal breathing and only acquiring data when the diaphragm is within a pre-defined acceptance window (Figure 5.1a). The trade-off of navigator gating is significantly increased scan duration because of poor navigator efficiency. For example, previous CMR studies have have reported respiratory navigator efficiencies of 20 to 45% in adults [71, 68, 69, 74]. This poor navigator efficiency lengthens the duration of currently used clinical imaging and limits clinical feasibility of emerging advanced imaging techniques.

Navigator efficiency is typically poor because breathing patterns can be erratic

[21, 22, 23] and the patient is generally unaware of the desired acceptance window

location. Providing the patient with visual feedback of the diaphragm position during CMR (”navigator feedback”)has been shown to improve breathing consistency and scan efficiency in adults [68, 21]. For example, studies have shown efficiency improvements up to 29% (absolute) compared to traditional acquisitions without feedback [68, 69]. Importantly, these previous studies have demonstrated that image quality from navigator feedback acquisitions is similar to acquisitions without feedback [68, 69]. The potential to achieve similar benefits using navigator feedback with pediatric participants has not been explored. Given the challenge of keeping these participants still and motionless for long periods of time, this improved efficiency could have substantial clinical benefit.

Most previous studies involving navigator feedback simply utilized the built-in navigator display. One previous study evaluated a custom videogame interface in a study of adults for increasing navigator efficiency [69]. Such an interface theoretically combines the benefits of visual feedback with an intuitive and engaging design for the user–attributes that are highly desirable for pediatric scanning. Thus, the present study sought to extend and tailor this paradigm specifically for children by providing navigator feedback in the form of an interactive, kid-friendly videogame. Moreover, this study sought to test this design using DENSE, an imaging technique that can be used to quantify advanced measures of function such as cardiac strains. We hypothesized that navigator feedback using an interactive videogame during CMR would improve navigator efficiency and maintain image quality and strains in children.

**5.3 Methods**

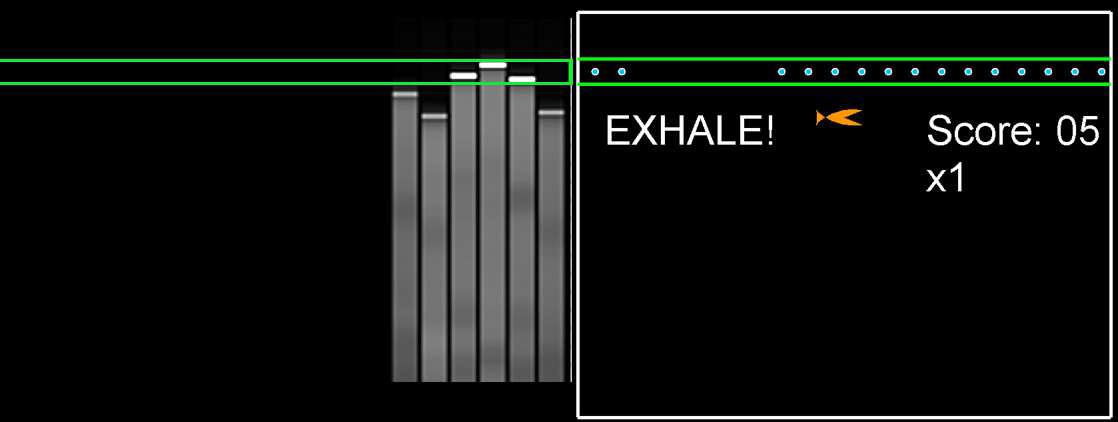
*5.3.1 Feedback videogame*

A navigator feedback videogame (FG), called ”Bubble Gulp”, was developed using MATLAB (The Mathworks Inc, Natick, MA). Each frame of the navigator

Cropped Siemens

Syngo Navigator Image

Acceptance Window



Exhale Direction

Diaphragm

Inhale Direction

A Position B

Example Frame of

Feedback Videogame Interface

Bubble Gulp

Instructions

- How to move fish

within acceptance window

**Figure 5.1: Feedback videogame.** (**A**) Cropped version of the Siemens Syngo navigator image that was processed in real-time during CMR acquisition to yield the feedback videogame. (**B**) Example frame of the navigator feedback videogame interface, which was shown to the child during CMR (yellow overlay text was not shown to the child).

image provided within the Siemens Syngo user-interface (Siemens Healthcare, Erlangen, Germany) (Figure 5.1a) was captured using an Epiphan DVI2USB 3.0 (Epiphan Systems Inc., Palo Alto, California) frame grabber and processed in real-time during CMR to yield a kid-friendly representation of the diaphragm position (Figure 5.1b). Navigator image processing was performed using an externally connected laptop running Windows 7 with an Intel Core i7 processor and

16 GB of RAM. The FG interface was then projected to the participant in the scanner using an angled mirror and a magnetic resonance compatible projector (Figure 5.2).

The diaphragm position relative to the acceptance window (Figure 5.1a) was represented by the vertical position of a fish character relative to parallel green lines containing scrolling dots, representing bubbles (Figure 5.1b). The objective of the game was to control the fish’s vertical position, which was updated with each navigator pulse, so it would ”gulp” bubbles and acquire points. To incentivize slow, stable breathing, point values increased as the fish spent more time within the green

MRI Scanner

MRI Scanner

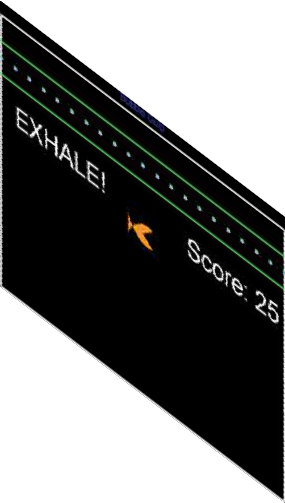
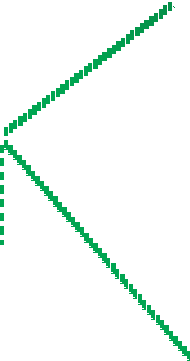
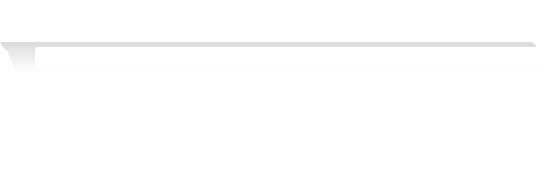
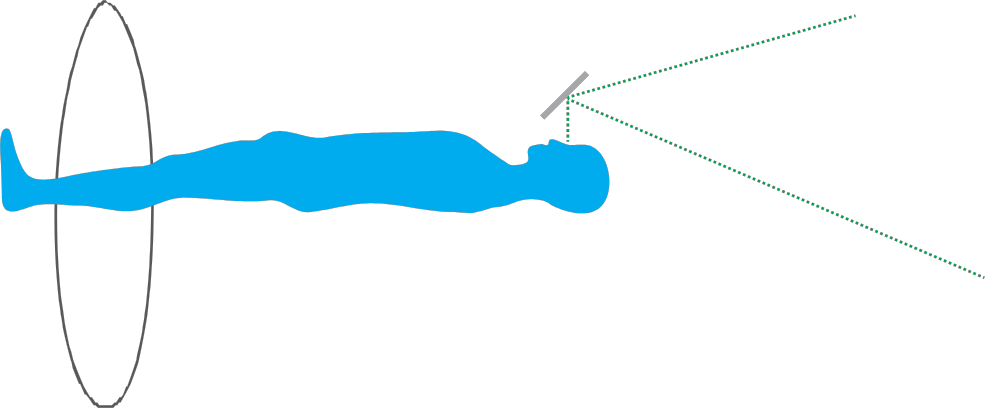
Mirror

Mirror

Feedback

Videogame

**Figure 5.2: MRI Feedback Setup** Feedback videogame was shown to children during CMR with an angled mirror and MR-compatible projector.



lines, instead of frequent short-duration breath-holds. However, prior to any use of the FG, children were instructed to not hold their breath for an uncomfortable amount of time and to breathe when needed. Finally, the FG interface displayed text to instruct children how to adjust their breathing in order to place the fish in between the green lines (Figure 5.1b).

*5.3.2 Participants*

Fifty children with no significant past medical history were recruited to participate in the study. Participants were recruited from the broader clinical community based out of our university medical center using a wide range of participant recruitment services provided by the University of Kentucky Center for Clinical and Translational Science. All participants were screened with a 12-lead ECG prior to imaging to rule out arrhythmias. The local Institutional Review Board at the University of Kentucky approved the study protocol and all participants and legal guardians provided written informed consent or assent.

*5.3.3 Imaging*

All imaging was performed using a 3T Siemens Tim Trio (Siemens Healthcare, Erlangen, Germany) with a 6-element chest coil and a 24-element spine coil. For

each participant, navigator-gated 2D spiral cine DENSE CMR [45, 46] images from mid-ventricular, 4-chamber, basal, and apical image orientations were separately acquired with no feedback (NF) and then while using the FG. No instructions regarding breathing were given for the NF acquisitions, thus participants were allowed to breathe naturally. Between acquisitions with NF and those with the FG, each participant underwent two 30-heartbeat practice scans to familiarize himself or herself with the FG.

DENSE imaging parameters included: number of spiral interleaves = 12, interleaves per beat = 2, FOV= 360 360 mm2, pixel spacing = 2.8 2.8 mm2,slice thickness = 8 mm, TE = 1.4 ms, TR = 17 ms, variable flip angle = 20*◦*, displacement encoding = 0.06 cyc/mm [6], through-plane dephasing = 0.08 cyc/mm [31], CSPAMM echo suppression [32], view sharing and a dual- navigator strategy

[30] with an acceptance window size of *±*3 mm. For each cardiac cycle, the

navigator echo occurred immediately after data acquisition. The dual-navigator strategy required the diaphragm position to be within the acceptance window for both the preceding *and* current cardiac cycles in order for data to be accepted. Prospective ECG gating was performed and 11–25 cardiac phases were acquired depending on participant heart rate. As a result of the imaging parameters, each complete image acquisition required 38 heartbeats that satisfied the navigator gating criteria.

Due to erratic respiratory patterns or participant movement, image acquisition can be difficult to complete in children in a reasonable amount of time with NF. As scan session duration increases, the likelihood of patient movement also increases, so we defined criteria for maintaining a target scan protocol duration of 30 min. We defined image acquisition as incomplete (data not acquired) following 192 heartbeats without a completed image acquisition. Progressing past 192 heartbeats for a 38- heartbeat scan is equivalent to achieving less than 20% navigator efficiency, which

is worse than previously reported NF values [71, 68, 69, 74]. Once any NF image acquisition was marked as incomplete, we proceeded to the FG acquisitions. If a participant moved, the number of acquired image orientations was reduced from four (mid, 4ch, base, apex) to two (mid, 4ch) to ensure at least two images were acquired with NF and FG.

*5.3.4 Calculation of cardiac strains from DENSE*

DENSE images were analyzed using *DENSEanalysis* [34], a custom, open-source MATLAB (the Mathworks Inc, Natick, MA) software. To delineate the myocardium, endocardial and epicardial boundaries were manually drawn on the DENSE magnitude image using an end-systolic and end-diastolic frame. The motion field was reconstructed using a simplified analysis technique [35]. Using manual selection of seed points, which indicated unwrapped phase data, a path-following algorithm was used to unwrap the displacement-encoded phase data. Temporal fitting and spatial smoothing was applied to the resulting Lagrangian displacements as previously described [36].

Two-dimensional segmental Lagrangian strains were quantified from the smoothed trajectories over the entire cardiac cycle. Radial and circumferential strain was computed for 6 myocardial segments of the short-axis images and longitudinal strain was computed from the long-axis images. The strain curves of all the cardiac segments were averaged into a single average curve. Global peak strain was quantified by averaging the strain curves from each slice and finding the resulting peak strain of this curve. When computing peak longitudinal strain, pixels within 10% of left ventricular longitudinal length of the most basal and apical regions were excluded due to increased noise typically observed in the strain curves in those regions. Peak strain was defined as a positive for thickening (radial strain) and negative for shortening (circumferential and longitudinal strain).

*5.3.5 Analysis*

This study measured navigator efficiency and heart rate during image acquisition and used image signal-to-noise ratio (SNR) of the end-systolic DENSE magnitude image as a measure of image quality. Navigator efficiency was defined as the ratio of the number of heartbeats for which image data were accepted to the total number of heart beats required to complete the image acquisition. To compare image quality, signal to noise ratio (SNR) was calculated for each cardiac phase of each DENSE magnitude image. SNR was computed from the average myocardium signal and the standard deviation of the signal (noise) within an area with no signal (free from tissue and imaging artifacts). Due to the Rician distribution of the MR signal, corrections were applied to the measured standard deviation (*σM* in Equation 5.1) and measured myocardial signal (*M* in Equation 5.2) to compute the true SNR [46, 6, 67]. The SNR was defined as the ratio of the true myocardial signal to the true standard deviation.

2

*σ* =

4 *− π*

*∗ σM ≈* 1*.*526 *∗ σM* (5.1)

*S* = *√M* 2 *− σ*2 (5.2)

For incomplete NF image acquisitions (satisfied stoppage criterion), navigator efficiency and heart rate measurements were computed based on the partial data that were acquired.

*5.3.6 Training*

Off-scanner training has been used by other investigators to ensure participants are comfortable and understand a navigator feedback interface before entering the magnet [68]. We wanted to determine the efficacy of off- scanner training with the FG on navigator efficiency, image quality, and heart rate. Thus, 30 of the 50 enrolled

participants were randomized into equal groups to either receive extensive off-scanner training or no off-scanner training prior to scanning; thus, the groups were referred to as ’trained’ and ’untrained.’ As mentioned above, all subjects (including trained and untrained participants) underwent minimal training in the scanner, which was defined as two 30-heartbeat practice scans prior to FG acquisitions. The remaining 20 participants also received off-scanner training, but they were not included within the trained subgroup for analysis because they were not randomized to this treatment.

Each trained participant was introduced to the FG using an MRI simulator prior to the formal study. The MRI simulator utilized a PrimeSense Carmine 1.09 (Prime- Sense, Tel Aviv, Israel) 3D camera to precisely measure the chest wall and abdomen excursion as a proxy for diaphragm translation [75, 76]. Each participant had to complete goal-based training before advancing to CMR scanning. Training time was recorded for all trained participants. The training protocol is described in detail in Appendix B.

*5.3.7 Statistics*

Statistical analyses were completed using R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). All continuous measurements were reported as mean *±* standard deviation. Navigator efficiency, SNR, heart rate, and global left ventricular strains were tested for normality using a Shapiro-Wilk test. Average navigator efficiency, SNR, heart rate, and strain were compared between NF and FG acquisitions using a paired student’s t-test or Wilcoxon Signed-Rank test when appropriate, and compared between untrained and trained groups using a student’s t-test or Mann-Whitney U test when appropriate. To determine whether age had an effect on navigator efficiency, age was correlated with navigator efficiency for both NF and FG acquisitions.

**5.4 Results**

Fifty-six children were prospectively enrolled. Six children were excluded from the study due to either being uncomfortable in an MRI scanner, having premature ventricular contractions, having ECG-monitoring equipment fail, or consistently moving during scanning. Thus, this study reported data on 50 children (Age: 14 *±*

3 years, 48% female) with no significant past medical history, which included a subset of 30 children randomized to either the off-scanner trained (n = 15; Age: 15

*±* 3 years, 47% female) or untrained (n = 15; Age: 13 *±* 3, 66% female) groups. All

trained participants successfully completed off-scanner training and the mean training duration was 11 *±* 2 min. The prescribed stoppage criterion for the NF scans was met in 11 cases, resulting in fewer completed NF images for those

participants. Additionally, four participants moved during scanning, which included two during NF scans and two during FG scans, resulting in the completion of the abridged imaging protocol, as described in the methods.

*5.4.1 Navigator Efficiency*

Using the FG significantly improved average navigator efficiency compared to NF (58 *±* 13% vs 33 *±* 15%, p *<* 0.001, Figure 5.3a). Average navigator efficiency was not correlated with age for either NF or FG image acquisitions (r = 0.07, p =

0.63; r=0.14, p = 0.32, Figure 5.3b). There was no significant difference in average navigator efficiency between untrained and off-scanner trained groups for FG image

acquisitions (57 *±* 17% vs 57 *±* 11%, p = 0.90, Figure 5.4).

*5.4.2 SNR*

Use of the FG significantly improved SNR compared to NF (22 *±* 6 vs 21 *±* 6, p

= 0.01, Figure 5.5). There was no significant difference in SNR between untrained and off-scanner trained groups for FG images (22 *±* 6 vs 21 *±* 6, p = 0.77).

100

Average Navigator Efficiency (%)

80

p < 0.001

100

80

NF, r = -0.07, p = 0.63

FG, r = 0.14, p = 0.32

60 60

Average Navigator Efficiency (%)

40 40

20 20

0 A 0 B

No

Feedback

Feedback

Game

8 10 12 14 16 18

Age (years)

**Figure 5.3: (A) Average navigator efficiency for No Feedback and Feedback Game image acquisitions.** Use of the feedback game significantly increased navigator efficiency compared to no feedback. The solid red line indicates the mean of each group. **(B) Average navigator efficiency vs age for No Feedback (NF) and Feedback Game (FG) image acquisitions.** There was no correlation between navigator efficiency and age for either no feedback (r = -0.07, p = 0.63) or feedback game (r = 0.14, p = 0.32) acquisitions. The solid lines indicate the line of best fit for each group.

100

Feedback Game

p = 0.90

80

Average Navigator Efficiency (%)

60

40

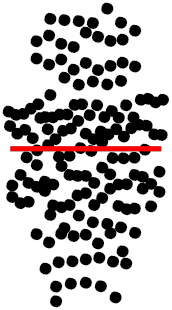
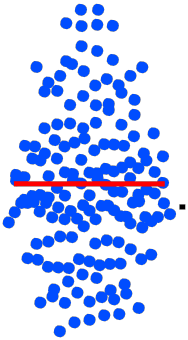
20

0

Untrained Trained

**Figure 5.4: Average navigator efficiency for Off-scanner Trained and Untrained groups.** There was no significant difference in navigator efficiency between untrained and off-scanner trained groups for feedback game acquisitions. The solid red line indicates the mean of each group.

45



p = 0.01

40

35

30

25

SNR

20

15

10

5

0 No

Feedback

Feedback

Game

**Figure 5.5: SNR for all No Feedback and Feedback Game images.** Use of the feedback game resulted in significantly increased SNR compared to no feedback.

110

100

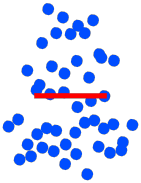
Mean Heart Rate (bpm)

90

80

25

p < 0.001 p = 0.30



20

Heart Rate Variability (bpm)

(Standard Deviation)

15

70 10

60

5

50

40

No

Feedback

Feedback

Game

0

No

Feedback

Feedback

Game

**Figure 5.6: Mean and standard deviation of heart rate for No Feedback and Feedback Game acquisitions.** Use of the feedback game resulted in significantly higher heart rate compared to no feedback. There was no significant difference in standard deviation of heart rate between no feedback and feedback game acquisitions. The solid red line indicates the mean of each group.

*5.4.3 Heart rate*

On average, heart rate during FG scans was slightly higher than NF acquisitions (75 *±* 13 vs 72 *±* 12 bpm, p *<* 0.001, Figure 5.6), but there were no differences in the standard deviation of heart rate (5.9 *±* 2.2 vs 6.1 *±* 3.9 bpm, p =0.30, Figure 5.6b). Heart rate was similarly elevated during FG acquisitions in both the untrained and off-scanner trained groups compared to NF acquisitions (p *<* 0.001 and p = 0.03, respectively, Table 5.1).

*5.4.4 Strain*

Global circumferential and radial strains derived from FG acquisitions were slightly lower in magnitude compared to NF acquisitions (16 *±* 2% vs 17 *±* 2%, p *<*

0.001; 40 *±* 10% vs 44 *±* 11%, p = 0.005, respectively, Table 5.2). There were no

77

**Table 5.1: Average Heart Rate for Off-scanner Trained and Untrained groups.**

HeartRate (bpm) Trained Untrained

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | No Feedback | Feedback Game | p-value | No Feedback | Feedback Game | p-value |
| Mean | 72 *±* 13 | 76 *±* 16 | 0.03 | 72 *±* 9 | 78 *±* 9 | *<* 0.001 |
| Standard Deviation | 6.9 *±* 5.0 | 5.7 *±* 2.4 | 0.80 | 5.3 *±* 2.4 | 6.0 *±* 2.0 | 0.17 |

**Table 5.2: Global peak strain results for NF and FG scans.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | No Feedback | Feedback Game | p-value |
| Circumferential Strain (%) Radial Strain (%) | -17 *±* 2  44 *±* 11 | -16 *±* 2  40 *±* 10 | *<* 0.001  0.005 |
| Longitudinal Strain (%) | -13 *±* 2 | -13 *±* 2 | 0.38 |

differences in longitudinal strain between NF and FG acquisitions (13 *±* 2% vs 13 *±*

2%, p =0.38).

**5.5 Discussion**

Feedback of the diaphragm position during CMR has been shown to improve navigator efficiency in adults [68, 69]. This study explored how the use of a feedback game (FG) affects navigator efficiency compared to traditional no- feedback (NF) acquisitions in children. The results of the study showed that, compared to NF, using the FG resulted in 1) substantially improved navigator efficiency (from 33 to

58%); 2) slightly improved SNR; 3) slightly higher mean heart rate; and 4) slightly lower global strain magnitudes. Importantly, these results were not affected by the use of an off-scanner training protocol, which suggests that lengthy, robust training (11 min in our protocol) does not need to be a part of the clinical/imaging workflow for this interface.

*5.5.1 Navigator Efficiency*

Navigator efficiency was improved from 33 to 58% by using a FG in children (Figure 5.3a). This increase in navigator efficiency led to a 43% reduction in the number of heartbeats required to complete a scan. Studies have shown that feedback of the diaphragm position during CMR results in a more reproducible breath-hold position [68, 69, 77], which can lead to improved navigator efficiency. Previous CMR studies have reported that NF navigator efficiencies can vary from 20 to 45% in adults [71, 68, 69, 74], and we found a comparable NF navigator efficiency of 33% in

children using a conservative dual-navigator acceptance strategy. Visual feedback of the diaphragm position has been shown to improve end-expiratory navigator efficiency from 45 to 56% [69] and from 42 to 71% with the addition of supplemental oxygen [68] leading to a 20% and 41% reduction in the number of required heartbeats, respectively. With the use of the FG, we found a slightly better improvement of navigator efficiency from 33 to 58% in children without the use of supplemental oxygen. Average navigator efficiency was not correlated with age (Figure 5.3b). Therefore, children ages eight and older should be able to utilize the FG to effectively improve navigator efficiency compared to conventional NF acquisitions.

Extensive off-scanner training using an MRI-simulator was not necessary to achieve the observed improvement in navigator efficiency using the FG. Instead, the subjects with minimal training immediately prior to data acquisition had equivalent efficiency as their extensively-trained counterparts. While this finding might suggest that the chest wall excursion-based training method was ineffective, it is more likely that the intuitive interface design was easy to learn and therefore the children did not require much training. Importantly, the two 30-beat practice scans provided some degree of training in both cases, which is intuitively necessary. Future efforts can optimize that practice time to provide the needed minimal training in the most efficient manner.

*5.5.2 SNR*

We found that using the FG slightly improved the SNR of the end-systolic magnitude images of our spiral DENSE sequence by 5% compared to NF for all images combined (p = 0.01, Figure 5.5). This finding contrasts with previous studies, which reported image quality score using 2 expert reviewers and found that the use of diaphragmatic feedback maintained image quality compared to NF acquisitions [68, 69]. The difference in image quality is likely sequence dependent. The previous studies were performed using steady-state free precession.

Additionally, it is likely that quantitative measurement of SNR is more sensitive at detecting differences in image quality compared to subjective image scoring by expert reviewers.

*5.5.3 Heart Rate*

A potential negative finding of this study was the slight increase in heart rate observed with the use of the feedback game. To be clear, this difference did not represent an increase in heart rate variabilityas evidenced by the comparable standard deviation valuesbut simply a higher baseline value. Such findings are not unprecedented, as a previous CMR study found a mean heart rate increase of 5 beats/min with use of navigator feedback in adults (compared to our 3 beats/min), and similarly no differences in heart rate variability between NF and navigator feedback [68]. A likely reason for this difference is the longer breath-holds performed during the FG, which could have increased the heart rate, compared to relaxed breathing during NF. Another mechanism could be related to stimulation and adrenaline associated with playing the game, compared to the relaxed, passive state associated with NF.

The importance and implications of this potential heart rate difference likely depends on the imaging application. While it may mean very little for purely anatomic evaluations, functional measures, such as strains, may be affected by changing loading conditions and contractility [78]. To counteract such effects, if undesirable, patients could be coached to relax when playing the game and to not be too competitive. The design of the game could be modified to enforce such behavior; for example, by programmatically requiring the participant to inhale/exhale after a fixed period of time, or instructing him/her to periodically take a series of relaxed breaths between cycles of breath-holding.

*5.5.4 Strains*

We observed small, but statistically significant decreases in global circumferential and radial strains with use of the FG, compared with NF. There was, however, no difference in longitudinal strain. While these findings warrant further study and consideration, the clinical relevance of such small differences (1% for circumferential strain, 4% for radial strain) is likely minimal as they are smaller than previously observed inter-test (*±*2.0% for circumferential, *±*13% for radial) and inter-observer (*±*1.4% for circumferential, *±*14% for radial) 95% limits of agreement for DENSE [46, 6].

*5.5.5 Clinical Implications*

Importantly, the equipment needed to utilize the FG is minimal and does not directly integrate into an imaging sequence; it connects externally to the scanner user interface. Due to the minimal equipment needed and non-invasive connection to the MRI scanner, we anticipate that the FG system can be easily adopted at research and clinical sites that perform CMR navigator gating, especially in children. Since navigator efficiency can be increased from 33 to 58%, leading to reduced acquisition times, use of the FG can help improve the clinical feasibility of advanced imaging techniques. While reducing the acquisition time would likely be the most common use of increased navigator efficiency from the FG, the saved time could be allocated to improve image spatial or temporal resolution [68]. Importantly, pre-scan training was not necessary for navigator efficiency improvement with our system, so clinical and research sites would not have to invest in an MRI simulator environment or spend significant time training children. Navigator feedback has been shown to reduce acquisition time in adults [68], thus, the use of the FG will likely work well in adults also.

Since we only acquired DENSE images for this study, the specific findings are

only definitively relevant for DENSE. However, it is reasonable to expect that these findings are generalizable to many other CMR acquisitions that utilize a respiratory navigator. Possible exceptions include higher resolution applications, such as coronary MR angiography, which may be more sensitive to registration issues. Further study is needed to test this technique for these applications.

*5.5.6 Comparison with Previous Work*

A previous study presented a respiratory biofeedback game and continuously adaptive windowing strategy (CLAWS) to increase navigator efficiency of imaging the thoracic aorta. The authors reported an increase in efficiency in that study from

45 to 56% in adults [69], which represents a smaller magnitude of improvement (25% vs 11%) but a similar end result (58% vs 56%) compared to our study. Although the two studies are similar, there are distinct differences in design. Most notably, the previous study was in adults; whereas we exclusively focused on children, based on their limited ability to breath-hold and thus potentially greater need for respiratory navigated sequences. Additionally, the previous study modified their pulse sequence to allow acquisition of multiple navigator echoes, likely providing a smoother game experience. We did not modify our cine pulse sequence in our evaluationwe had a single navigator echo per cardiac cyclein order to ensure more general clinical applicability. Collectively, these studies demonstrate the potential utility of user-friendly interfaces for improving efficiency and image quality of cardiovascular imaging sequences using a respiratory navigator in a broad array of patients.

*5.5.7 Limitations*

This study used a dual-navigator strategy when performing image acquisition. Dual-navigator strategies have stricter data acceptance criteria compared to previously used single-navigator strategies [45], and, given the same imaging parameters, will likely result in lower navigator efficiencies. However, a previous

study using a single-navigator strategy with navigator feedback reported similar navigator efficiency results compared to our study. Therefore, the use of the FG with a single- navigator strategy will likely have similar results to this study except that both NF and FG acquisitions may have improved navigator efficiency compared to a dual-navigator strategy.

The respiratory navigator gating sequence used in this study only measured the diaphragm position once per cardiac cycle. This low refresh rate can make fine control of the diaphragm position more challenging, especially for participants who may have lower heart rates. Increasing the number of navigator echoes per cardiac cycle could therefore improve performance, but such modifications may not be possible for all sequences, as is the case for DENSE. Furthermore, even with this limitation, we still found substantial improvement in navigator efficiency when using the FG compared to NF acquisitions.

Due to the randomization of the participants into the trained and untrained groups, there was no attempt to balance age between groups. Therefore, the average trained participant was about 2 years older than the average untrained participant. We found that there was no difference in FG navigator efficiency between trained and untrained participants. Even though there was an age difference between trained and untrained groups, there was no correlation between age and navigator efficiency with the FG (Figure 5.3b); thus, the results of the study apply to all children aged eight to eighteen.

In order to accurately assess the NF navigator efficiency as it would be in the clinical setting, we did not want to influence the children’s natural breathing pat- tern. In particular, we did not want the breathing pattern performed during the FG acquisitions to influence the NF breathing pattern. Therefore, NF acquisitions were always performed before FG acquisitions. Since the order of NF and FG acquisitions was not randomized, this may have affected the results as participants may have

become more comfortable as they spent more time in the MRI scanner. However, performing this randomization likely would have resulted in similar conclusions and we feel that it was important to accurately measure the navigator efficiency of the NF acquisitions.

Due to the potential for patient movement or erratic breathing patterns, we utilized a stoppage criterion to attempt to maintain a 30 min protocol length. We observed eleven cases which satisfied stoppage criterion and four cases of patient movement (one which also satisfied stoppage criterion). In these participants, we estimated navigator efficiency, SNR, and heart rate from fewer acquisitions than the remaining participants. However, since we used all of the data that we did acquire for each participant, the computed values are appropriate.

The two 30-heartbeat practice scans were not included in the computation and analysis of navigator efficiency for the FG technique. Their inclusion would only slightly decrease the reported gains in efficiency (for example, if we used the FG to acquire 300 heart beats of actual data, the reduction in scan time would change minimally from 43 to 37% after accounting for the two practice scans); however, it must be noted that the selection of those practice parameters was arbitrary and not optimized. In reality, less training is likely required to familiarize the subject with the interface, so factoring this specific training design into the analysis is not critical.

We performed this study in children with no significant past medical history. While we did attempt to recruit from a broad clinical population using recruitment services at our Center for Clinical and Translational Science, the population we ultimately studied may not be entirely representative of a standard pediatric clinical population that would routinely undergo cardiac MRI. For example, approximately

25% of patients with tetralogy of Fallot may have learning and behavioral difficulties [79], which may impair their ability to benefit from the feedback game. It is therefore reasonable to expect that the true benefit of the feedback game in a

standard clinical population will be smaller than what was measured in the current study, but still better than what can be expected without the use of feedback. Even if only half of the patients benefit to the extent shown in the current study, the overall navigator efficiency for the clinical population as a whole would still increase from 33% efficiency to 46% efficiency (a 38% relative benefit). Future research will seek to evaluate this in further detail as we implement the feedback game during routine clinical workflows.

*5.5.8 Conclusion*

Use of a respiratory navigator feedback game designed to engage children during navigator-gated CMR improved navigator efficiency in children from 33 to 58%. This improved efficiency reduces the number of heartbeats and corresponding scan durations by 43%, and is also associated with a 5% increase in SNR for spiral cine DENSE. Pre-scan training on how to use the feedback game is not necessary to achieve the improvement in navigator efficiency. These findings should generalize to all CMR acquisition sequences that utilize a respiratory navigator.

**Appendices**

**APPENDIX A**

**DIFFERENCES IN SEGMENTAL STRAIN BETWEEN DIFFERENT ACCEPTANCE WINDOW POSITIONS**

**Table A.1: Segmental circumferential strain (%, mean** *±* **standard deviation) from the three acceptance window**

**positions (minimum, middle, and maximum) for all subjects combined.**

Anterior Anteroseptal Inferoseptal Inferior Inferolateral Anterolateral

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Strain** | **P** | **Strain** | **P** | **Strain** | **P** | **Strain** | **P** | **Strain** | **P** | **Strain** | **P** |
|  |  |  |  |  | **Basal** |  |  |  |  |  |  |
| **Max** | -16*±*5 |  | -14*±*5 |  | -14*±*5 |  | -15*±*5 |  | -19*±*6 |  | -19*±*5 |  |
| **Mid** | -16*±*3 | 0.99 | -13*±*5 | 1.0 | -15*±*5 | 0.95 | -15*±*5 | 0.91 | -18*±*5 | 0.88 | -19*±*5 | 0.76 |
| **Min** | -15*±*4 |  | -13*±*5 |  | -15*±*4 |  | -15*±*5 |  | -19*±*6 |  | -18*±*4 |  |

**Mid-Ventricular**

**Max** -17*±*5

-14*±*5

-13*±*5

-17*±*5

-22*±*6

-20*±*6

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Mid** | -17*±*5 | 0.93 | -14*±*4 | 0.83 | -14*±*4 | 0.87 | -18*±*5 | 0.93 | -21*±*4 | 1.0 | -21*±*6 | 0.81 |
| **Min** | -17*±*6 |  | -14*±*4 |  | -13*±*4 |  | -17*±*3 |  | -20*±*5 |  | -21*±*6 |  |
|  |  |  |  |  |  | **Apical** |  |  |  |  |  |  |

**Max** -18*±*5

**Mid** -18*±*5

0.66

-15*±*6

-15*±*5

0.99

-17*±*6

-17*±*6

0.79

-20*±*6

-20*±*6

0.98

-23*±*7

-23*±*6

0.84

-22*±*6

-22*±*7

0.99

**Min** -18*±*6 -15*±*5 -16*±*6 -21*±*6 -24*±*6 -21*±*7

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**Table A.2: Segmental radial strain (%, mean** *±* **standard deviation) from the three acceptance window positions**

**(minimum, middle, and maximum) for all subjects combined.**

Anterior Anteroseptal Inferoseptal Inferior Inferolateral Anterolateral

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Strain** | **P** | **Strain** | **P** | **Strain** | **P** | **Strain** | **P** | **Strain** | **P** | **Strain** | **P** |
|  |  |  |  |  | **Basal** |  |  |  |  |  |  |
| **Max** | 37*±*20 |  | 36*±*16 |  | 40*±*20 |  | 43*±*23 |  | 47*±*29 |  | 41*±*21 |  |
| **Mid** | 40*±*21 | 0.78 | 41*±*18 | 0.61 | 37*±*14 | 0.53 | 36*±*21 | 0.77 | 47*±*31 | 0.94 | 44*±*24 | 0.64 |
| **Min** | 38*±*18 |  | 38*±*17 |  | 37*±*18 |  | 40*±*22 |  | 51*±*29 |  | 46*±*28 |  |

**Mid-Ventricular**

**Max** 28*±*17

33*±*24

34*±*15

32*±*15

36*±*32

32*±*17

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Mid**  **Min** | 31*±*19  30*±*19 | 0.94 | 35*±*19  36*±*14 | 0.44 | 31*±*13  36*±*16 | 0.88 33*±*24  31*±*21 | 0.96 | 38*±*29  35*±*24 | 0.83 | 33*±*18  28*±*17 | 0.49 |
|  |  |  |  |  |  | **Apical** |  |  |  |  |  |
| **Max** | 28*±*24 |  | 36*±*37 |  | 41*±*21 | 41*±*37 |  | 31*±*23 |  | 27*±*16 |  |
| **Mid** | 23*±*12 | 0.72 | 31*±*13 | 0.87 | 39*±*20 | 0.83 40*±*20 | 0.20 | 27*±*17 | 0.84 | 26*±*15 | 0.69 |
| **Min** | 25*±*15 |  | 35*±*24 |  | 40*±*27 | 34*±*24 |  | 29*±*20 |  | 33*±*16 |  |

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**APPENDIX B**

**SEGMENTAL STRAINS FOR NAVIGATOR GATING**

**B.1 Peak Segmental Strains for Navigator Gating and Breath-holds**

The myocardium was divided into 6 segments for mid-ventricular short-axis images and 7 segments for four-chamber long-axis images based on the American Heart Association 17-segment model. The peak strain was computed for each segment and reported using mean and standard deviation of all segments in Table S1. For four-chamber images, pixels from the most basal and apical segments (3 segments in total) were excluded from analysis in order to remove the increased noise typically observed in those regions, which also matched the analysis performed for global longitudinal strain.

**B.2 Segmental Strain Agreement Between Navigator Gating and Breath- holds**

Peak segmental strains were compared between each navigator gating configuration (retrospective, prospective, and dual) and breath-holds using Bland-Altman analyses and coefficient of variation (CoV). Comparisons were performed using a paired Students t-test.

**Table B.1: Segmental strain results for navigator gating and breath-holds in adults.**

**Circumferential Strain (%)**

**Mean** *±* **Std. Dev.**

Breath-hold -18 *±* 5

Retrospective -18 *±* 5

Prospective -18 *±* 5

Dual -18 *±* 4

**Radial Strain (%)**

Breath-hold 35 *±* 16

Retrospective 34 *±* 16

Prospective 42 *±* 17

Dual 34 *±* 16

**Longitudinal Strain (%)**

Breath-hold -13 *±* 4

Retrospective -14 *±* 3

Prospective -13 *±* 3

Dual -14 *±* 4

**Table B.2: Segmental strain agreement between navigator gating and breath-holds from spiral cine DENSE.**

**Radial Strain (%)**

**Longitudinal Strain (%)**

\* indicates p *<* 0.05

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Bias** | **95% LoA** | **CoV (%)** | **p-value** |
| **Circumferential Strain (%)** |  |  |  |  |
| Retrospective–Breath-hold | 0 | *±* 5 | 8 | 0.94 |
| Prospective–Breath-hold | 0 | *±* 8 | 13 | 0.78 |
| Dual–Breath-hold | -1 | *±* 5 | 8 | 0.11 |
| Retrospective–Breath-hold | 0 | *±* 25 | 19 | 0.79 |
| Prospective–Breath-hold | 8 | *±* 36 | 28 | 0.002\* |
| Dual–Breath-hold | -1 | *±* 29 | 23 | 0.61 |
| Retrospective–Breath-hold | -1 | *±* 7 | 13 | 0.17 |
| Prospective–Breath-hold | 0 | *±* 9 | 17 | 0.75 |
| Dual–Breath-hold | -1 | *±* 8 | 13 | 0.19 |

**APPENDIX C**

**OFF-SCANNER TRAINING PROTOCOL FOR FEEDBACK GAME C.1 Training Protocol**

The goal-based training protocol was as follows: First, the children were

instructed to perform 3 sequential end-expiratory breath-holds to determine the optimal location for the acceptance window. Then the children were instructed to complete 9 levels of the FG, which progressed in difficulty. Difficulty was increased by either 1) decreasing the acceptance window size or 2) increasing the time delay between chest excursion recording and fish location update. Because the navigator gating sequence only measures the diaphragm position during each heartbeat, children with slower heartbeats may experience ”delays” between diaphragm movement and fish location update. In order to complete each level, the children had to acquire 100 points. If all bubbles were acquired in a row with no breaks, each level could be completed in *∼*33 seconds.

**C.2 Survey Responses**

In order to formally measure the enjoyment and response of the children playing the Feedback Game, we asked the children to fill out a post-scan survey that consisted of 7 questions. Those questions and responses are listed below. In general, most participants 1) found Bubble Gulp to be easy to play; 2) enjoyed playing Bubble Gulp;

3) thought they were generally getting better as they played; 4) thought training was/would have been somewhat helpful; 5) had no comments on how to improve

’Bubble Gulp’; 6) enjoy playing videogames; and 7) play videogames daily.

**Question 1 Response**

12

10

8

Number of Children

6

4

2

0

**Figure C.1:** Question 1. How easy was playing Bubble Gulp?

1: Really easy

2: Easy

3: Neither easy nor difficult

4: Difficult

5: Really Difficult

**Question 2 Response**

15

Number of Children

10

5

0

**Figure C.2:** Question 2. How much did you enjoy playing Bubble Gulp?

1: Really enjoyed it

2: Enjoyed it

3: Neither

4: Did not enjoy it

5: Really did not enjoy it

**Question 3 Response**

15

10

Number of Children

5

0

**Figure C.3:** Question 3. Did you think you were getting better, stayed the same, or were getting worse as you were playing Bubble Gulp at the end of the study compared to when you first tried it?

1: Better

2: Stayed the same

3: Worse

**Question 4 Response**

15

10

Number of Children

5

0

**Figure C.4:** Question 4. We have a pretend MRI scanner where you can learn to play Bubble Gulp before getting into the actual MRI scanner. Do you think using this pretend MRI scanner first would have been/was:

1: Very helpful

2: Somewhat helpful

3: Not helpful

4: A total wast of time

5. Do you have any comments on how to improve Bubble Gulp?

*•* Mostly ”None”

*•* ”Make the fish pink”

*•* ”Make the lines further a part on the screen”

*•* ”Liked the simple concept and how could control with breathing”

*•* ”Reverse direction of fish movement with breathing”

*•* ”Make not as glitchy, (make smoother)”

*•* ”Make lines move to more comfortable spot to breathe in”

**–** This subject moved before their last scan

**Question 6 Response**

20

15

Number of Children

10

5

0

**Figure C.5:** Question 6. How much do you enjoy playing videogames?

1: Really enjoy

2: Enjoy

3: Neither

4: Do not enjoy

5: Really do not enjoy

**Question 7 Response**

15

Number of Children

10

5

0

**Figure C.6:** Question 7. How often do you play videogames?

1: Daily

2: 2-3 times per week

3: Weekly

4: 1-2 times per month

5: Seldom to never

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