Title

Three Dimensional Speckle Tracking Based Strain Imaging Identifies Alterations in Dynamic Left Ventricular Function after Cardiac Surgery

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Three Dimensional Speckle Tracking Based Strain Imaging Identifies Alterations in Dynamic Left Ventricular Function after Cardiac Surgery

A thesis submitted in partial satisfaction of the requirement for the degree

Masters of Science in Clinical Research

by

Kimberly Howard-Quijano

2014

ABSTRACT OF THE THESIS

Three Dimensional Speckle Tracking Based Strain Imaging Identifies Alterations in Dynamic Left Ventricular Function after Cardiac Surgery

by

Kimberly Howard-Quijano

Masters of Science in Clinical Research

University of California, Los Angeles 2014

Professor Robert M. Elashoff, Chair

Three-dimensional (3D) echocardiography based strain imaging is an emerging modality to assess dynamic left ventricular function in patients undergoing cardiac surgery.

Adult patients undergoing cardiac surgery (n=182) were prospectively imaged with 3D transthoracic echocardiograms (TTE) pre- and post-operatively and analyzed for left ventricular 3D; ejection fraction (EF), global peak systolic area (GAS), longitudinal (GLS), circumferential (GCS), and radial (GRS) strain. 3D strain correlated well with 3D EF. Receiver operating curves identified 3D GAS as the best indicator for ventricular function, with a normal cutoff of -25%. Pre-operative 3D strain was an independent predictor of ICU stay and inotrope score, increasing predictive value of known pre-operative risk factor models, especially in patients with reduced ventricular function. Demonstrating that after cardiac surgery, there is an acute reduction in post-operative left ventricular function that can be accurately measured with 3D speckle tracking strain imaging and strain measures may be predictive of post-operative outcomes

The thesis of Kimberly Howard-Quijano is approved.

Aman Mahajan

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Janet S. Sinsheimer

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Introduction

Over half a million cardiac surgeries are performed in the United States each year and left ventricular systolic function is a strong predictor of their outcomes. [1] While open heart surgery with cardiopulmonary bypass (CPB) is an essential life saving operation, it can lead to diminished post-operative cardiac function. [2] Following bypass, there is an acute decrease in ventricular function due to delayed recovery of myocardial performance after reperfusion. [3] These changes in ventricular function can cause hemodynamic instability in the acute postoperative period requiring escalating inotropic support, prolonged hospital stay, and long-term complications including, increased risk for inpatient morbidity and mortality.

Systolic cardiac function has routinely been assessed using echocardiography and two-dimensional (2D) left ventricular ejection fraction (LVEF) calculations. These traditional measurements have variable accuracy and are based on mathematical assumptions of left ventricular (LV) geometry. [4] Through recent advances in echocardiography, strain as a measure of myocardial tissue deformation, can now be investigated as an indicator of both regional and global myocardial function. [5-8] Strain imaging has been shown to measure ventricular function with better accuracy and reliability then traditional (2D) LVEF calculations in a variety of non-surgical patients with varying degrees of ventricular dysfunction. [4,9 10, 11, 12,13] Macron et al, demonstrated that in patients with poor acoustic windows, strain values correlated more closely with ventricular function assessed from magnetic resonance imaging than traditional echocardiography LVEF measurements.[14] Speckle tracking strain imaging using newly developed three-dimensional (3D) echocardiography is an improvement over previous 2D strain measurements as speckle tracking is no longer limited to motion in the imaging plane. [15,12,10]

3D strain may provide new insight into the acute changes in LV myocardial function associated with varying open-heart surgical procedures, which has not previously been studied. The primary aim of this study is to investigate changes in global left ventricular function after cardiac surgery using 3D speckle tracking strain imaging. We hypothesize that ventricular function, measured by strain, will be reduced in the acute period after cardiac surgery and that 3D strain will correlate with 3D volume based ejection fraction measurements of ventricular function. The secondary aims of this study are to: 1) investigate the changes in LV systolic function associated with differing cardiac surgical interventions including aortic valve, mitral valve, and coronary artery bypass operations and 2) to determine if pre-operative 3D strain is predictive of outcomes after cardiac surgery.

Methods

After institutional review board approval and informed consent, adult patients schedule for elective cardiac surgery between October 2011 and July 2013 at the Ronald Reagan UCLA Medical Center were enrolled in this prospective observational study. Surgical interventions included; aortic valve replacement for aortic stenosis (AVR), mitral valve repair or replacement for mitral regurgitation (MVR), coronary artery bypass graft (CABG), and combined multiple valve, CABG/valve, or AVR/aortic surgery for aortic insufficiency (Combined). Exclusion criteria were arrhythmias (such as atrial fibrillation), congenital heart disease, and poor transthoracic echocardiography imaging windows.

Clinical Data Collection

Preoperative (age, gender, and European System for Cardiac Operative Risk Evaluation score (EuroSCORE), intraoperative, and postoperative data were collected.[16] Definitions of all data variables collected were per the Adult Cardiac Surgery Database Training Manual, v2.73. Postoperative outcome variables were; duration of tracheal intubation (from intensive care admission to extubation), length of intensive care unit (ICU) stay, length of hospital stay, inotrope score, and major adverse events. Inotrope score, in the first 24 hours after ICU admission, was calculated using the vasoactive-inotrope score described by Wernovsky and expanded by Gaies. [17, 18] Major cardiac adverse events (MAE) per the Society of Thoracic Surgeons database were; cardiac arrhythmias (ventricular tachycardia, ventricular fibrillation, and asystole), multiple organ failure, ventricular assist device (balloon pump, or extracorporeal membrane oxygenation), and re-operation.

Echocardiography

Two transthoracic echocardiograms (TTE) were performed, a preoperative TTE in awake spontaneously ventilating patients on the day of surgery and a post-operative TTE 48-72 hours after surgery, once participants were extubated, with chest tubes and inotropic support discontinued. All echocardiographic studies were performed by the same experienced sonographer. Each patient underwent standardized 3D TTE for the determination of LV functional parameters according to the American Society of Echocardiography, 3D images were taken with Vivid 9, GE healthcare with a 3V transducer at frame rate of 25-55 frame/sec.

Three-dimensional speckle tracking analysis

The 3D Echocardiogram data acquisition was obtained in an adjustable imaging sector volume, with breath hold lasting 4 heart beats. Images were recorded at the LV apex with minimal volume size to ensure optimal temporal and spatial resolution. Data analysis was preformed offline by one of three experienced blinded echocardiographers using 4D Auto LVQ for semi automated endocardial surface detection, with manual adjustments of automatic tracing if needed. Final 3D software output included measurement of global area, longitudinal circumferential, and radial strain. (Figure 1)

Reproducibility Analysis

32 cases (20% of patients) were randomly selected and assessed for intraobserver and interobserver reliability. Intraobserver reliability was assessed by the same echocardiographer, blinded to the previous results, analyzing each study again, greater than 2 weeks from date of original study. Two expert echocardiographers greater than 1 week apart, blinded to the previous results, evaluated interobserver reliability. Reliability agreement was measured using Bland-Altman plots, reported as mean difference (bias) ± 95% confidence intervals (precision).

Statistical Analysis

Histograms and quartile plots were examined in a bivariate analysis to determine whether distributions of continuous outcomes were reasonably modeled by a Gaussian distribution (parametric) on the normal scale, or after transformation to log scale. Measures of central tendency for parametric data were reported as mean (± standard deviation) and non-parametric data as median (interquartile range).

The correlation between each strain parameter and 3D volume based EF was measured using Pearson correlation coefficients. 3D volume based EF has been shown to be closely correlated with MRI based measures of ventricular function and was used in this study as the reference point to compare the other measures of ventricular function. [12, 19] Correlations were done on all patients comparing pre- and post-operative EF with each pre- and post-operative strain parameter.

The mean difference between pre-operative and post-operative ventricular function, as measured by EF and strain, were compared using paired t-tests. Differences between pre-and post-operative measures within the surgical categories were tested using repeated measures analysis of variance (ANOVA) and Tukey's honestly significant difference (HSD) test. Differences in outcomes between surgical groups were assessed using non-parametric Wilcoxon test for multiple comparisons.

Receiver operating characteristic (ROC) curves were performed for each type of strain, to determine the cut-off value for normal (EF>50%), mild-moderate reduction (EF<45%), or severely reduced (EF<35%) ventricular function.[9, 20, 21] Each cut-off value was chosen using Wald technique to maximize accuracy. The accuracy was defined as the average of the sensitivity and specificity (accuracy = 0.5 sensitivity + 0.5 specificity). For each strain parameter; the area under the curve, 95% confidence interval, sensitivity, and specificity are reported. Mean differences in outcomes in patients with normal versus abnormal ventricular function were measured using non-parametric Mann-Whitney U test for continuous outcomes and Fishers exact test for dichotomous outcome measures.

The relationship between primary outcomes (length of stay, duration of intubation, and inotrope score) and strain variables was assessed using linear multiple regression models. A log transformation was done on outcome variables to normalize distribution. Pre-operative predictor variables of EUROSCORE and surgical procedure were used to construct linear regression prediction models for the primary outcomes. Due to high co-linearity between strain measures, global area strain (GAS), global longitudinal strain (GLS), circumferential strain (GCS), and global radial strain (GRS), were each added individually to separate models to see if they could independently contribute to predicting outcome variables given the known covariates. Models were examined in patients with EF <45% and EF >45%. Statistical analyses were run using R version 3.0.2 (www.r-project.org <http://www.r-project.org>) and SPSS 22 (IBM Corp., Armonk, NY). Post-hoc corrections were made for multiple hypothesis testing. Statistical significance was defined as $p \leq 0.05$.

Results

In total, 182 patients were enrolled in this study. Fourteen patients had echocardiography studies unsuitable for speckle tracking strain imaging (10 for post-operative arrhythmias, 4 technically difficult studies), 4 patients refused post-operative TTE, and 1 lost to follow-up. Data on 163 patients were analyzed; AVR=45, MVR=45, CABG=50, and Combined=23. Of patients undergoing aortic valve surgery, 38% had a bicuspid aortic valve. The medians for; patient age=63 years, weight=77 kilograms, pre-operative EUROSCORE=1.7, cardiopulmonary bypass times=134 min, and post-operative APACHE II score upon admission to ICU=9 out of a possible 299. (Table 1)

Comparison of Different Measures of Ventricular Function: Ejection Fraction and Strain

3D strain measurements were well correlated with volume based EF calculations for all strain measures. There was no significant difference between EF and strain correlations when looking at pre- versus post-operative measures of ventricular function. (Figure 2)

Pre- versus Post-Operative Ventricular Function: Changes in Ejection Fraction and Strain

Ejection fraction as measured by 3D echocardiography significantly decreased after surgery with collective mean pre-operative measurements of 47% as compared to post-operative 40%. Speckle tracking strain imaging measurements also decreased with preoperative mean values of; (3D) GAS= -25%, GLS= -13%, GCS= -17%, GRS=41% as compared to post-operative values of GAS= -18%, GLS= -9%, GCS= -11%, GRS=25% respectively, with all post-operative reductions being statistically significant ($p<0.005$).

By surgical subdivision (AVR, MVR, CABG, Combined), the only statistically significant pre-operative differences were increased measures of ventricular function in MVR as compared to all other surgical groups, likely due to the reduced afterload associated with mitral regurgitation. There was no difference seen after surgical repair. A reduction in ventricular function was seen after surgery across all surgical subgroups. (Table 2). However, there was a significant difference in the mean magnitude of change between the surgical groups. The largest magnitude of reduction (3D EF) was seen after MVR (23%) and combined procedures (21%), with the smallest reduction after AVR (9%) and CABG (7%). The same difference in magnitude of reduction by surgical subgroup analysis was seen across all strain measurements as well.

Receiver Operating Characteristic (ROC) Curves

ROC curves were constructed for each measure of 3D peak systolic global strain (GAS, GLS, GCS, and GRS) to determine a threshold value for normal ventricular function (EF>50%), mild to moderately reduced ventricular function (EF<45%), and severely reduced function (EF<35%). Global area strain (GAS) had the best performance characteristics for determining ventricular function (Figure 3). GAS threshold value of – 25% was associated normal ventricular function, with an area under the curve (AUC) of 0.86 (95% CI; 0.81-0.89), - 21% with mild to moderate reduced function AUC 0.85 (0.81-0.89), and -18% with severely reduced ventricular function AUC 0.89 (0.85-0.93).

Post-Operative Outcomes

Post-operative outcome measures for study cohort can be seen in table 3. Collectively, the median ICU stay (LOS_{ICU}) was 4 days, hospital stay ($LOS_{Hospital}$) was 7 days, duration of intubation was 6 hours, highest inotrope score was 3, and 18% of patients suffered from a major adverse event (MAE). The subgroup of Combined surgical procedures had significantly worse outcomes with higher inotrope score than AVR, longer length of ICU stay and intubation than AVR and MVR, and longer hospital stay and MAEs than all groups, $p < 0.05$. (Table 3)

Association Between Clinical Outcomes and Pre-operative Strain

Using 3D GAS cut-point of – 25%, patients were dichotomized into normal versus abnormal ventricular function prior to surgical intervention. Patients with abnormal pre-operative measures of GAS had longer length of ICU stay (LOS_{ICU}: 4 vs. 3 days), length of total hospitalization

($LOS_{Hospital}$: 7 vs. 6 days), and length of post-operative intubation (7 vs. 5 hrs). There was no significant difference in post-operative inotrope score (3 vs. 2) or major adverse events (10.3% vs. 8.5%). (Table 4)

Pre-operative Strain as a Predictor of Post-Operative Outcomes

Multivariate regression analyses showed pre-operative strain measures are independent predictors of post-operative outcomes including; length of ICU stay and increased inotrope score, after controlling for clinical predictors (EUROSCORE and surgery type). In addition strain adds predictive value to clinical risk factor models, as reported by model r^2 values, in table 5. Pre-operative strain was found to be more beneficial in predicting outcomes in patients with reduced pre-operative ventricular function (EF <45%).

In patients with pre-operative EF >45%; pre-operative all 3D strain types were independently associated with length of ICU stay. Clinical predictors alone produced a baseline model r^2 value of 0.22 for length of ICU stay. The addition of strain independently increased the model predictive value up to 32% as demonstrated by increased r^2 values; GAS = 0.29, GCS = 0.29, GLS 0.26, and GRS = 0.28 ($p<0.05$).

In patients with reduced pre-operative ventricular function (EF<45%), pre-operative GAS, GCS, and GRS were independently associated with increased length of ICU stay, and all strain types were independently associated with inotrope score after surgery. When predicting increasing length of ICU stay; clinical factors alone produced baseline r^2 value of 0.26, with the addition of pre-operative strain predictive r^2 values increased up to 31%: GAS = 0.32, GCS = 0.34, GRS =

0.33 ($p<0.05$). Strain was also independently associated with inotrope score after cardiac surgery and increased predictive value of models up to 68%; baseline $r^2 = 0.22$, with strain: GAS = 0.33, GCS = 0.37, GLS =0.28, GRS = 0.36 ($p< 0.05$). Pre-operative strain was not found to be an independent predictor of duration of intubation.

Reproducibility Analysis

There was good intra- and inter-rater reliability observed for both pre and post-operative 3D EF and strain analysis; reported as mean difference (bias) and 95% confidence interval as ± two standard deviations (precision), as shown in table 6.

Discussion

Changes in left ventricular function after cardiac surgery have important prognostic implications and influence clinical decision-making. The results of this study show that in the acute period after cardiac surgery, there is a reduction in ventricular function that was accurately measured with 3D speckle tracking TTE strain imaging. In addition, pre-operative strain was shown to be an independent predictor of acute post-operative outcomes, especially in patients with reduced ventricular function.

Speckle tracking via 3D echocardiography is a new imaging modality to measure myocardial strain, which is no longer limited to tracking only in the imaging plane. 3D strain allows concurrent measurement of longitudinal, circumferential, radial strain, and a new measurement unique to 3D, area strain. 3D echocardiography allows faster, more reliable measures of strain, with increased accuracy and reproducibility. [22-24] The results of our study show that all measures of global strain correlate well with 3D EF and accurately measure the associated dynamic changes in ventricular function associated with cardiac surgery.

When comparing different strain measures, longitudinal strain was found to have a slightly lower correlation with 3D ejection fraction (EF) than area, circumferential and radial strain. This is supported by work in non-surgical patients, where Luo found 3D global area strain had the highest correlation to EF.[8] While Luis et al, found global circumferential strain to have the highest correlation in patients with varying ejection fractions.[22] There was no difference in strain and EF correlations due to pre-operative surgical diagnoses, after varying surgical procedures, or between pre and post-operative exams. Therefore for the first time, this study shows that 3D strain is an accurate measure of ventricular function in patients with valvular and ischemic cardiac disease, as well as, after complex surgical repairs and prosthetic valve placement.

Using traditional imaging modalities, it has been described that long term myocardial function improves after AVR for aortic stenosis and decreases after MVR for mitral regurgitation.[25, 26] However, the acute post-operative changes in ventricular mechanics still remain undefined. For example, in patients undergoing AVR for aortic stenosis, the results of studies using 2D strain are inconclusive. One week after AVR, Rost et al, showed no significant change, whereas, Carasso et al, demonstrated an increase in post-operative 2D strain.[25, 27]

In this study, we were able to evaluate and characterize these acute post-operative ventricular changes associated with cardiac surgery, using 3D strain imaging. The results of this study show that there was a significant reduction in ventricular function immediately following cardiac surgery in all surgical subgroups, with the smallest reduction in ventricular function after AVR for aortic stenosis and CABG for ischemic coronary artery disease. In contrast, the largest reduction in function was seen after MVR for mitral regurgitation. The difference between the acute versus long-term changes in observed ventricular function may be seen because strain is a remodeling-dependent parameter. Changes in acute ventricular function may be more dependent on intra- and acute post-operative management then immediate hemodynamic changes associated with valvular surgery.[25] The observation in this study that there is an acute reduction in ventricular function immediately following all types of cardiac surgery suggests that this is an area requiring further investigation to help define ways to improve intra-operative and post-operative management of patients undergoing cardiac surgery.

There are no studies to date defining reference values for 3D strain in patients with normal, mild-moderate, and severely reduced ventricular function. Our results show that while the receiver operating curve characteristics vary slightly with strain type, global area strain performs the best across varying degrees of ventricular function. Global area strain reflects the changes in endocardial surface area with LV contraction and incorporates simultaneous changes in longitudinal, circumferential, and radial strain.[28] Patients with pre-operative ventricular dysfunction, as defined by reduced 3D global area strain, had worsening post-operative outcomes and pre-operative 3D strain was found to be an independent predictor of these outcomes. The addition of 3D strain measurements to multivariate pre-operative risk models increased the predictive value for length of ICU stay by up to 32% and post-operative inotrope score up to 68%. The greatest increase in predictive value was seen in patients with pre-operative ventricular dysfunction.

Pre-operative strain was shown to be an independent predictor for length of ICU stay in all patients. Increased length of ICU stay is indicative of prolonged recovery and leads to increased utilization of hospital resources. Reduced pre-operative EF has been demonstrated to increase post-operative morbidity and mortality and prolong patient recovery after cardiac surgery. [29] This finding of pre-operative strain as a predictor of length of ICU stay, even in patients with normal ventricular function, as defined by EF, demonstrates the potential for strain measures to be a valuable addition to current risk stratification for patients undergoing cardiac surgery.

Pre-operative strain was also found to be an independent predictor of post-operative inotrope score. Inotrope score is a pharmacologic measure of cardiovascular support. Increasing amounts of cardiovascular support after cardiac surgery have been associated with higher likelihood of postoperative complications. [18] We found that strain was a predictor of inotrope score in patients with reduced ventricular function, but not in those starting with normal cardiac function. These results suggest that patients with normal ventricular function, have more myocardial reserve. Thus, the use of inotropes post-operatively is less dependent on the starting ventricular function, and likely; more dependent on other factors associated with the surgical procedure or related complications. Pre-operative strain was not found to be an independent predictor for post-operative duration of intubation. This lack of association is likely due to the confounding variables of baseline pulmonary status, pain control and narcotic administration, as well as, residual anesthetics, which play a large role in the clinical decision regarding extubation timing.

Limitations

This study included patients undergoing a variety of cardiac surgical procedures, which lends to increased applicability of results across patients. However, the heterogeneity of the study cohort and smaller numbers in surgical subgroups may not provide adequate power to detect all differences between groups. While this study was able to measure acute changes in left ventricular function after cardiac surgery, long-term follow-up is needed to determine the association between changes in acute post-operative function and long-term ventricular function.

The use of 3D speckle tracking strain imaging to detect changes in ventricular function, is associated with improved speckle tracking and strain measurement however, the decreased frame rate associated with full-volume image acquisition, leads to decreased temporal resolution. While 3D strain analysis has been shown to require significantly less time to analyze than traditional 2D strain imaging, it requires off line analysis, which is a limitation. Advances in technology will likely soon alleviate this limitation.

Conclusions

This study demonstrates that in patients undergoing a wide variety of cardiac surgical procedures, there is an acute reduction in post-operative left ventricular function that can be accurately measured with 3D speckle tracking strain imaging. Pre-operative 3D strain was found to be an independent predictor of acute post-operative outcomes, especially in patients with reduced pre-operative ventricular function. The use of non-invasive 3D TTE strain imaging prior to cardiac surgery may provide added information to aid in risk stratification for these high-risk patients, thus improving patient care and allocation of resources.

Tables

Table 1. Demographic data by surgical classification				
	Aortic Valve (n=45)	**Mitral Valve (n=45)**	**Coronary Artery Bypass (n=50)**	**Combined (n=23)**
Age (years)	65 (56-74)	62 (52-71)	64 (57-72)	63 (43-70)
Gender (%)	M=33 (73%) F=12 (27%)	M=28 (62%) F=17 (38%)	M=41 (82%) F=9 (18%)	M=18 (78%) F=5 (22%)
Weight (kg)	77 (68-88)	74 (57-83)	76 (68-86)	77 (69-88)
Height (cm)	172 (162-177)	170 (162-179)	168 (163-177)	167 (165-174)
EUROSCORE II	1.4 (0.7-2.2)	1.4 (0.7-2.2)	1.9 (1.2-3.0)	3.6 (1.9-8.8)
CPB time (min)	124 (101-151)	178 (122-218)	109 (88-127)	180 (146-224)
APACHE Score	9 (7-12)	8 (7-10)	10 (8-15)	11 (6-16)

Data reported as median and interquartile range (IQR). EUROSCORE= European System for Cardiac Operative Risk Evaluation Score, APACHE = Acute physiology and chronic health evaluation II score, CPB = cardiopulmonary bypass

Table 2. Ventricular function measurements by surgical classification				
	Aortic Valve (n=45)	**Mitral Valve (n=45)**	**Coronary Artery Bypass (n=50)**	**Combined (n=23)**
Ejection Fraction (%)				
	Pre vs. Post (% Change)	**Pre vs. Post** (% Change)	**Pre vs. Post** (% Change)	**Pre vs. Post** (% Change)
3D EF	43±10 vs. **39±9*** (9%)	53±10 vs. **41±13*‡** (23%)	46±9 vs. **43±11*** (7%)	47±8 vs. **37±14*** (21%)
3D Peak Systolic Global Strain (%)				
	Pre vs. Post	**Pre vs. Post**	**Pre vs. Post**	**Pre vs. Post**
Area	-22±7 vs. **-17±6*** (23%)	-30±7 vs. **-20±7*†** (33%)	-24±6 vs. **-17±7*** (29%)	-27±7 vs. **-16±6*†** (41%)
Longitudinal	-10±4 vs. **-9±3*** (20%)	-15±6 vs. **-11±4*†** (33%)	-12±4 vs. **-9±4*** (25%)	-14±4 vs. **-9±4*** (36%)
Circumferential	-15±5 vs. **-10±4*** (33%)	-19±4 vs. **-12±5*‡** (37%)	-15±4 vs. **-11±5*** (33%)	-17±5 vs. **-9±5*‡** (47%)
Radial	35±14 vs. **24±10*** (29%)	51±17 vs. **29±12*‡** (43%)	37±13 vs. **24±12*** (35%)	42±13 vs. **22±10*†** (45%)

Data reported as mean ± standard deviation, *=p<0.05 for significant reduction in post-operative ventricular function. **†** = % Difference > AVR, **‡** = % Difference > AVR and CABG. EF = Ejection fraction.

Table 3. Outcome measures by surgical classification				
	Aortic Valve (n=45)	**Mitral Valve (n=45)**	**Coronary Artery Bypass (n=50)**	**Combined (n=23)**
LOS $_{ICU}$ (days)	4 (2-5)	3 (2-5)	5 (3-5)	**5 (3-9)***
LOS $_{Hospital}$ (days)	6 (5-8)	7 (5-7)	6 (5-9)	**9 (7-16)†**
LOI (hours)	5 (3-8)	5 (4-8)	7 (5-10)	**10 (5-20)***
Inotrope Score	1 (0-5)	0 (0-7)	3 (0-9)	**7 (3-13)‡**
Major Adverse Events (%)	Y=6 (13%)	Y=2 (4%)	Y=11 (22%)	**Y=11 (48%)†**

Data reported as median (IQR), LOS = length of stay, LOI = length of intubation, ICU = Intensive care unit
***=**Combined > AVR/MVR, **†=**Combined > AVR/MVR/CABG, **‡=**Combined > AVR ($p<0.05$)

Table 4. Post-operative outcomes in patients with normal versus decreased pre-operative 3D Global Area Strain			
	Normal	**Reduced**	**p-value**
ICU Length of Stay (days)	3 (1-18)	**4 (1-19)**	**p = 0.002***
Hospital Length of Stay (days)	6 (3-36)	**7 (3-27)**	**p = 0.03***
Length of Intubation (hours)	5 (0-318)	**7 (2-191)**	**p = 0.01***
Inotrope Score	2 (0-38)	3 (0-26)	p = 0.14
Major Adverse Events (%)	8.5%	10.3%	p = 0.89

Data reported as median (IQR) or percentages. Reduced 3D global area strain defined as < -25%. ICU = Intensive care unit

Table 5. Pre-operative 3D strain measures in multivariate prediction models of post-operative outcome measures					
	Length of ICU Stay		**Inotrope Score**		**Duration of Intubation**
EF>45% (n=105)	**r^2**		**r^2**		**r^2**
Clinical Predictors	0.22		0.16		0.22
Clinical Predictors + Pre-op 3D Strain (% improvement)					
Area	**0.29****	(32%)	0.16		0.25
Circumferential	**0.29****	(32%)	0.16		0.25
Longitudinal	**0.26***	(18%)	0.16		0.24
Radial	**0.28****	(27%)	0.16		0.25
EF<45% (n=58)					
Clinical Predictors	0.26		0.22		0.08
Clinical Predictors + Pre-op 3D Strain (% improvement)					
Area	**0.32***	(23%)	**0.33***	(50%)	0.12
Circumferential	**0.34***	(31%)	**0.37****	(68%)	0.12
Longitudinal	0.31	(19%)	**0.28***	(27%)	0.10
Radial	**0.33***	(27%)	**0.36****	(64%)	0.13

Clinical predictors: EUROSCORE and surgery type. Pre-operative global strain measures as independent variables in addition to baseline model. EF= ejection fraction. * = p<0.05, ** = p<0.001

Table 6. Intraobserver and interobserver reliability of 3D Ejection Fraction (EF) and global strain measurements		
	Pre-Operative (Mean difference ± SD)	**Post-operative** (Mean difference ± SD)
Intraobserver		
EF (%)	-0.34 ± 6.68	0.06 ± 4.53
Area (%)	0.27 ± 2.81	-0.04 ± 2.36
Longitudinal (%)	0.48 ± 2.05	-0.55 ± 1.64
Circumferential (%)	-0.16 ± 1.58	0.26 ± 1.76
Radial (%)	-0.84 ± 5.62	0.89 ± 3.27
Interobserver		
EF (%)	-1.38 ± 6.45	-0.88 ± 6.13
Area (%)	0.12 ± 2.80	0.11 ± 2.79
Longitudinal (%)	-0.06 ± 2.34	0.08 ± 2.01
Circumferential (%)	0.25 ± 2.14	0.02 ± 2.11
Radial (%)	-0.86 ± 6.58	-0.15 ± 4.24

SD = Two standard deviations

Figures/Figure Legend

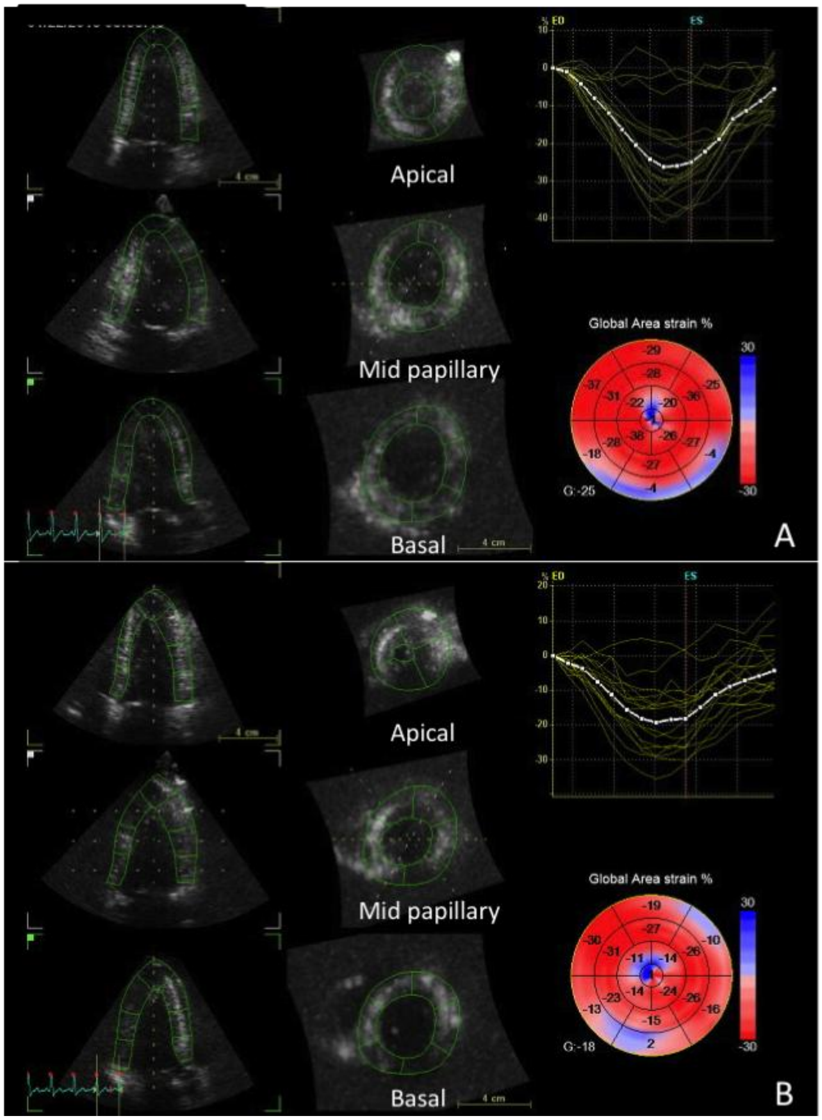


Figure 1. 3D left ventricular global area strain diagram depicting pre-operative results (panel A) and post-operative results (panel B), following mitral valve replacement.

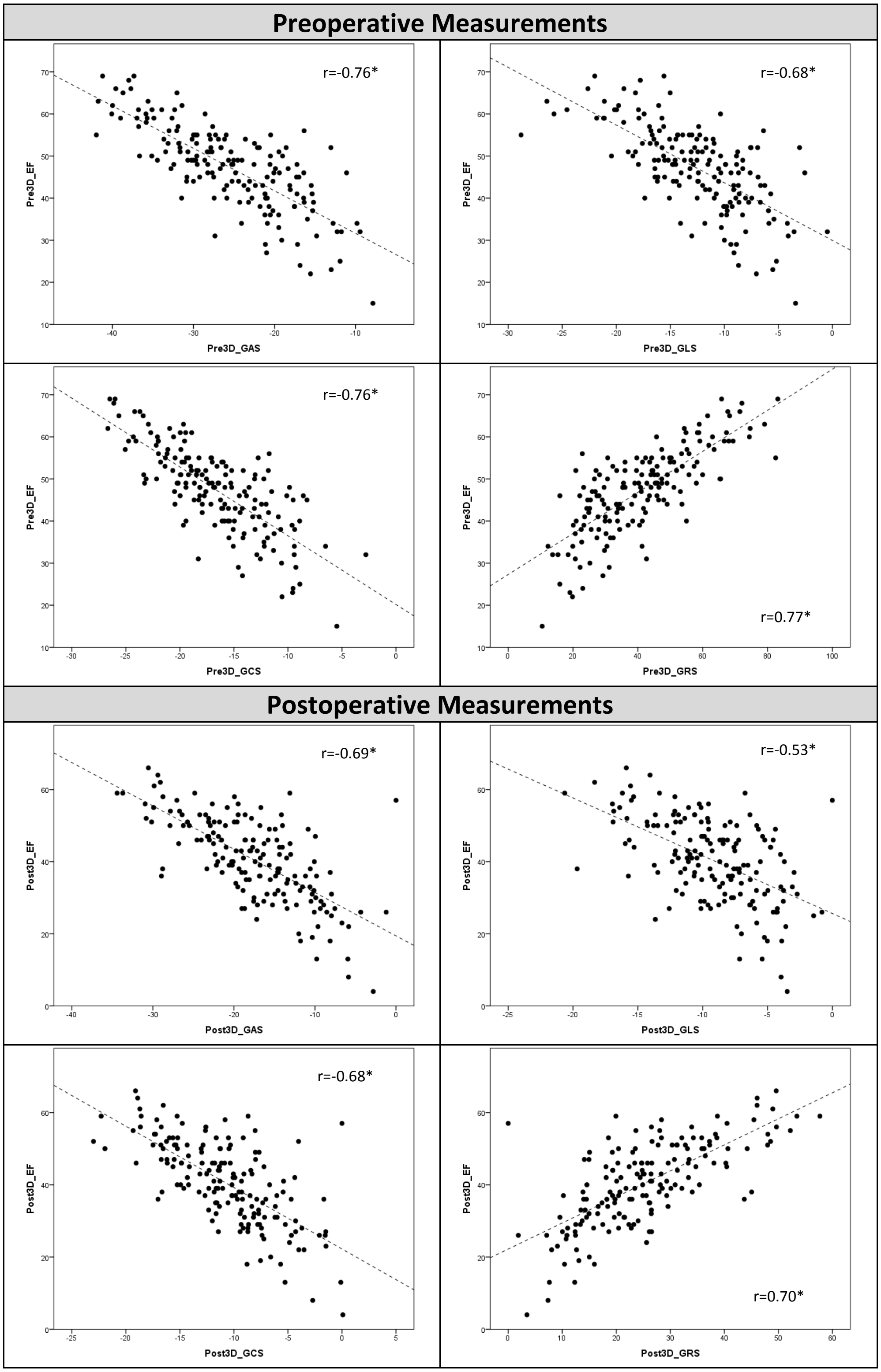
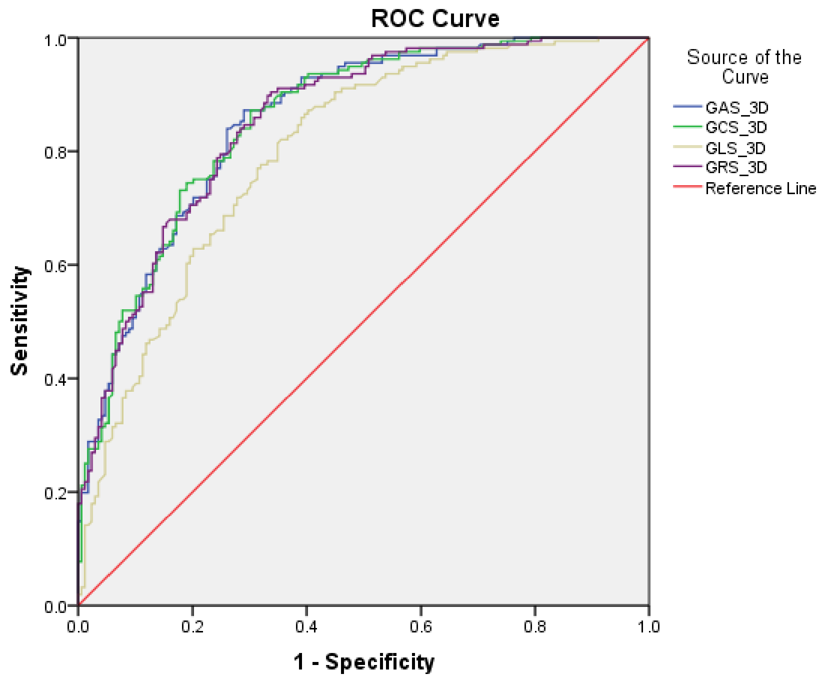


Figure 2. Scatterplots depicting correlation between 3D ejection fraction (EF) and GAS =area strain, GLS=longitudinal strain, GCS=circumferential strain, and GRS=radial strain.



Strain Measure	Area Under Curve (95% CI)	Threshold Value	Sensitivity and Specificity	
EF 50% - Normal				
3D GAS	0.86 (0.81-0.89)	- 25	85%	70%
3D GLS	0.82 (0.77-0.87)	- 12	79%	71%
3D GCS	0.84 (0.80-0.89)	- 16	80%	73%
3D GRS	0.86 (0.82-0.90)	35	81%	75%
EF 45% - Mild to Moderate Reduction				
3D GAS	0.85 (0.81-0.89)	- 21	84%	74%
3D GLS	0.80 (0.75-0.85)	- 11	78%	67%
3D GCS	0.86 (0.20-0.90)	- 14	83%	72%
3D GRS	0.85 (0.81-0.89)	32	83%	72%
EF 35% - Severe Reduction				
3D GAS	0.89 (0.85-0.93)	- 18	82%	78%
3D GLS	0.83 (0.78-0.88)	- 9	76%	73%
3D GCS	0.89 (0.85-0.93)	- 11	81%	82%
3D GRS	0.89 (0.85-0.93)	24	81%	81%

Figure 3. Receiver Operating Characteristics Curves (ROC) demonstrating 3D global area (GAS), longitudinal (GLS), circumferential (GCS), and radial strain, as determinants of ventricular function; normal (EF > 50%), mild to moderate reduction (EF < 45%), and severe reduction (EF < 35%).

Statistical Appendix

Study Design

This was a prospective observational cohort study designed to investigate the new technology of three-dimensional (3D) speckle tracking strain imaging to determine changes in left ventricular function after cardiac surgery. This prospective study design was chosen to allow control over subject enrollment and ensure equal distribution of patients undergoing different classifications of surgical procedures. This study design was also necessary, as this is new technology, and there is no available database of 3D echoes to investigate retrospectively. Patients were followed as a cohort after surgery to establish a chronologic sequence of events between changes in ventricular function and post-operative outcomes in order to determine the association of pre-operative ventricular function with post-operative outcomes.

Patients enrolled had a wide variety of pre-operative ejection fractions, as well as, several different classifications of valvular lesions to enable results to be generalized to a large population of cardiac surgical patients. However, care was taken during data analysis to perform subgroup analyses and ensure that the pre-operative differences in physiology, that could be confounding variables, were adequately addressed.

Three-dimensional Ejection Fraction and Strain Correlations

Pearson correlation matrices were analyzed to examine the relationship between each strain parameter and our reference three-dimensional (3D) volume based ejection fraction (EF %). EF and 4 global strain parameters were measured for each patient during pre and post-operative echocardiograms. Correlations were analyzed separately for pre and post-operative measures to determine the potential for differential association with EF and each strain parameter before and after surgery. Expanded correlation matrices show the different relationship between 3D EF and each strain measure for pre versus post-operative exams. (Appendix figures 1 and 2)

The correlations were also investigated by performing a subgroup analysis of patients with normal versus reduced ventricular function (EF<45%). There was a difference in the magnitude of the correlation between EF and strain for the collective cohort, as compared to the subgroup analysis. For example the pre-operative correlation for global area strain and EF was r=0.76 for all patients. However, subgroup analysis demonstrated EF>45% r=0.65 and EF<45% r=0.55. The difference in correlations seen between subgroups, and the collective cohort, is likely due to mild differential associations between the subgroups. Expanded correlation matrices between normal and reduced ventricular function groups, are shown in Appendix figures 3-6. Correlation scatter plots between pre-operative EF and strain measures, showing subgroup differences are shown in Appendix figure 7.

Regression Models

Multivariate regression analysis, controlling for known pre-operative risk factors, was performed to determine if each 3D strain parameter was an independent predictor of post-operative outcomes including; length of ICU stay, inotrope score, and duration of intubation. As the above correlation matrices show, strain parameters were very highly correlated and as such combining them into one model would result in unstable regression coefficients. Therefore, each model was run individually with each of the 4 strain parameters separately, for each of the three outcome variables. The r^2 of a baseline model with known pre-operative risk factors for each outcome was calculated. The preoperative risk factors were fixed in model and then the change in r^2 with the addition of each strain parameter was calculated, to determine the additional predictive value that each strain parameter may add to our known risk factor models. Detailed methods and results of the above models are described in text and shown in Chapter 1, table 6. Log transformations were applied to each outcome variable after analyzing histograms of distribution (Appendix Figure 8). Log transformation decreased the degree to which data was skewed and therefore decreased possible deviations from model assumptions (normality, homoscedasticity).

Principal Components Analysis

Principal components analysis was run to test the effect of combining the multiple (correlated) strain measurements into one predictor variable. Principal components analysis used orthogonal transformation to convert our set of highly correlated 4 global strain parameters into a set of linearly uncorrelated values or principal components. This transformation is defined such as the first principal component has the largest possible variance and accounts for the largest variability in each outcome and then each succeeding component has the highest variance under the constraints that is orthogonal to the preceding components. The results of the principle components analysis (PCA1) did not show dramatic increase in predictive value above and beyond the multivariate regression analysis models and therefore was not included in manuscript for publication; however results are shown in Appendix tables 1-3.

Tables

Appendix Table 1. Length of ICU Stay					
Type	Variables	R^2	p-val	R^2 log	p-val log
Baseline*		0.25		0.29	
3D	EF	0.26	0.31	0.32	0.11
	GAS	0.30	0.05	0.36	0.02
	GCS	0.32	0.02	0.36	0.02
	GLS	0.28	0.14	0.34	0.04
	GRS	0.31	0.03	0.36	0.02
	PCA1	0.31	0.04	0.35	0.02

Appendix Table 2. Inotrope Score					
Type	Variables	R^2	p-val	R^2 log	p-val log
Baseline*		0.24		0.25	
3D	EF	0.37	0	0.44	0
	GAS	0.3	0.03	0.36	0
	GCS	0.33	0.01	0.39	0
	GLS	0.27	0.1	0.32	0.02
	GRS	0.33	0.01	0.39	0
	PCA1	0.36	0	0.4	0

Appendix Table 3. Duration of Intubation					
Type	Variables	R^2	p-val	R^2 log	p-val log
Baseline*		0.05		0.11	
3D	EF	0.06	0.53	0.11	0.93
	GAS	0.06	0.59	0.15	0.11
	GCS	0.05	0.88	0.15	0.13
	GLS	0.07	0.44	0.14	0.17
	GRS	0.06	0.54	0.16	0.07
	PCA1	0.05	0.91	0.14	0.21

Figures

		Pre2D_EF	Pre2D_GLPS	Pre2D_GLCS	Pre2D_Global_PS_Circ	Pre2D_Global_PS_Radial	Pre3D_EF	Pre3D_GAS	Pre3D_GCS	Pre3D_GLS	Pre3D_GRS
Pre2D_EF	Pearson Correlation	1	-.719**	-.349**	-.367**	.391**	.653**	-.589**	-.626**	-.492**	.595**
	N	165	165	165	165	165	165	165	165	165	165
Pre2D_GLPS	Pearson Correlation	-.719**	1	.385**	.383**	-.373**	-.690**	.709**	.724**	.630**	-.712**
Pre2D_GLCS	Pearson Correlation	-.349**	.385**	1	.951**	-.640**	-.373**	.391**	.397**	.335**	-.392**
Pre2D_Global_PS_Circ	Pearson Correlation	-.367**	.383**	.951**	1	-.689**	-.407**	.407**	.413**	.356**	-.414**
Pre2D_Global_PS_Radial	Pearson Correlation	.391**	-.373**	-.640**	-.689**	1	.406**	-.377**	-.380**	-.337**	.401**
Pre3D_EF	Pearson Correlation	.653**	-.690**	-.373**	-.407**	.406**	1	-.761**	-.757**	-.678**	.765**
Pre3D_GAS	Pearson Correlation	-.589**	.709**	.391**	.407**	-.377**	-.761**	1	.929**	.929**	-.985**
Pre3D_GCS	Pearson Correlation	-.626**	.724**	.397**	.413**	-.380**	-.757**	.929**	1	.737**	-.927**
Pre3D_GLS	Pearson Correlation	-.492**	.630**	.335**	.356**	-.337**	-.678**	.929**	.737**	1	-.916**
Pre3D_GRS	Pearson Correlation	.595**	-.712**	-.392**	-.414**	.401**	.765**	-.985**	-.927**	-.916**	1

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Appendix Figure 1. 3D EF and strain correlations: All patients, pre-op measurements

		Post2D_EF	Post2D_GLPS	Post2D_GLCS	Post2D_Global_PS_Circ	Post2D_Global_PS_Radial	Post3D_EF	Post3D_GAS	Post3D_GCS	Post3D_GLS	Post3D_GRS
Post2D_EF	Pearson Correlation	1	-.566**	-.394**	-.360**	.330**	.500**	-.414**	-.428**	-.308**	.417**
	N	165	165	165	165	165	165	165	165	165	165
Post2D_GLPS	Pearson Correlation	-.566**	1	.391**	.350**	-.424**	-.630**	.673**	.594**	.632**	-.703**
Post2D_GLCS	Pearson Correlation	-.394**	.391**	1	.953**	-.667**	-.300**	.331**	.346**	.262**	-.345**
Post2D_Global_PS_Circ	Pearson Correlation	-.360**	.350**	.953**	1	-.686**	-.291**	.321**	.345**	.240**	-.334**
Post2D_Global_PS_Radial	Pearson Correlation	.330**	-.424**	-.667**	-.686**	1	.276**	-.371**	-.331**	-.328**	.389**
Post3D_EF	Pearson Correlation	.500**	-.630**	-.300**	-.291**	.276**	1	-.697**	-.691**	-.544**	.701**
Post3D_GAS	Pearson Correlation	-.414**	.673**	.331**	.321**	-.371**	-.697**	1	.907**	.850**	-.978**
Post3D_GCS	Pearson Correlation	-.428**	.594**	.346**	.345**	-.331**	-.691**	.907**	1	.560**	-.886**
Post3D_GLS	Pearson Correlation	-.308**	.632**	.262**	.240**	-.328**	-.544**	.850**	.560**	1	-.845**
Post3D_GRS	Pearson Correlation	.417**	-.703**	-.345**	-.334**	.389**	.701**	-.978**	-.886**	-.845**	1

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Appendix Figure 2. 3D EF and strain correlations: All patients, post-op measurements

		Pre3D_EF	Pre3D_GAS	Pre3D_GCS	Pre3D_GLS	Pre3D_GRS	Pre2D_EF	Pre2D_GLPS	Pre2D_GLCS	Pre2D_Global_PS_Circ	Pre2D_Global_PS_Radial
Pre3D_EF	Pearson Correlation	1	-.650**	-.654**	-.570**	.695**	.415**	-.455**	-.165	-.224*	.240*
	N	100	100	100	100	100	100	100	100	100	100
Pre3D_GAS	Pearson Correlation	-.650**	1	.898**	.915**	-.982**	-.403**	.566**	.308**	.317**	-.268**
Pre3D_GCS	Pearson Correlation	-.654**	.898**	1	.660**	-.899**	-.441**	.550**	.291**	.313**	-.260**
Pre3D_GLS	Pearson Correlation	-.570**	.915**	.660**	1	-.898**	-.311**	.520**	.271**	.277**	-.239*
Pre3D_GRS	Pearson Correlation	.695**	-.982**	-.899**	-.898**	1	.427**	-.581**	-.316**	-.336**	.303**
Pre2D_EF	Pearson Correlation	.415**	-.403**	-.441**	-.311**	.427**	1	-.532**	-.170	-.202*	.250*
Pre2D_GLPS	Pearson Correlation	-.455**	.566**	.550**	.520**	-.581**	-.532**	1	.134	.143	-.129
Pre2D_GLCS	Pearson Correlation	-.165	.308**	.291**	.271**	-.316**	-.170	.134	1	.965**	-.604**
Pre2D_Global_PS_Circ	Pearson Correlation	-.224*	.317**	.313**	.277**	-.336**	-.202*	.143	.965**	1	-.639**
Pre2D_Global_PS_Radial	Pearson Correlation	.240*	-.268**	-.260**	-.239*	.303**	.250*	-.129	-.604**	-.639**	1

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Appendix Figure 3. 3D EF and strain correlations: Pre-op measurements for patients with normal pre-operative ventricular function (EF>45%)

		Post3D_EF	Post3D_GAS	Post3D_GCS	Post3D_GLS	Post3D_GRS	Post2D_EF	Post2D_GLPS	Post2D_GLCS	Post2D_Global_PS_Circ	Post2D_Global_PS_Radial
Post3D_EF	Pearson Correlation	1	-.668**	-.684**	-.520**	.676**	.484**	-.583**	-.270**	-.249*	.235*
	N	100	100	100	100	100	100	100	100	100	100
Post3D_GAS	Pearson Correlation	-.668**	1	.923**	.869**	-.973**	-.403**	.618**	.284**	.266**	-.301**
Post3D_GCS	Pearson Correlation	-.684**	.923**	1	.622**	-.896**	-.446**	.549**	.349**	.349**	-.304**
Post3D_GLS	Pearson Correlation	-.520**	.869**	.622**	1	-.862**	-.277**	.617**	.184	.145	-.240*
Post3D_GRS	Pearson Correlation	.676**	-.973**	-.896**	-.862**	1	.400**	-.659**	-.294**	-.276**	.313**
Post2D_EF	Pearson Correlation	.484**	-.403**	-.446**	-.277**	.400**	1	-.596**	-.354**	-.322**	.287**
Post2D_GLPS	Pearson Correlation	-.583**	.618**	.549**	.617**	-.659**	-.596**	1	.285**	.240*	-.324**
Post2D_GLCS	Pearson Correlation	-.270**	.284**	.349**	.184	-.294**	-.354**	.285**	1	.959**	-.627**
Post2D_Global_PS_Circ	Pearson Correlation	-.249*	.266**	.349**	.145	-.276**	-.322**	.240*	.959**	1	-.627**
Post2D_Global_PS_Radial	Pearson Correlation	.235*	-.301**	-.304**	-.240*	.313**	.287**	-.324**	-.627**	-.627**	1

**. Correlation is significant at the 0.01 level (2-tailed).

Appendix Figure 4. 3D EF and strain correlations: Post-op measurements for patients with normal pre-operative ventricular function (EF>45%)

		Pre3D_EF	Pre3D_GAS	Pre3D_GCS	Pre3D_GLS	Pre3D_GRS	Pre2D_EF	Pre2D_GLPS	Pre2D_GLCS	Pre2D_Global_PS_Circ	Pre2D_Global_PS_Radial
Pre3D_EF	Pearson Correlation	1	-.545**	-.536**	-.465**	.529**	.529**	-.614**	-.410**	-.444**	.377**
	N	59	59	59	59	59	59	59	59	59	59
Pre3D_GAS	Pearson Correlation	-.545**	1	.889**	.885**	-.979**	-.478**	.644**	.294*	.291*	-.189
Pre3D_GCS	Pearson Correlation	-.536**	.889**	1	.595**	-.902**	-.554**	.711**	.349**	.331*	-.260*
Pre3D_GLS	Pearson Correlation	-.465**	.885**	.595**	1	-.858**	-.360**	.487**	.187	.205	-.115
Pre3D_GRS	Pearson Correlation	.529**	-.979**	-.902**	-.858**	1	.512**	-.676**	-.297*	-.295*	.230
Pre2D_EF	Pearson Correlation	.529**	-.478**	-.554**	-.360**	.512**	1	-.707**	-.352**	-.364**	.343**
Pre2D_GLPS	Pearson Correlation	-.614**	.644**	.711**	.487**	-.676**	-.707**	1	.526**	.494**	-.483**
Pre2D_GLCS	Pearson Correlation	-.410**	.294*	.349**	.187	-.297*	-.352**	.526**	1	.925**	-.646**
Pre2D_Global_PS_Circ	Pearson Correlation	-.444**	.291*	.331*	.205	-.295*	-.364**	.494**	.925**	1	-.716**
Pre2D_Global_PS_Radial	Pearson Correlation	.377**	-.189	-.260*	-.115	.230	.343**	-.483**	-.646**	-.716**	1

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

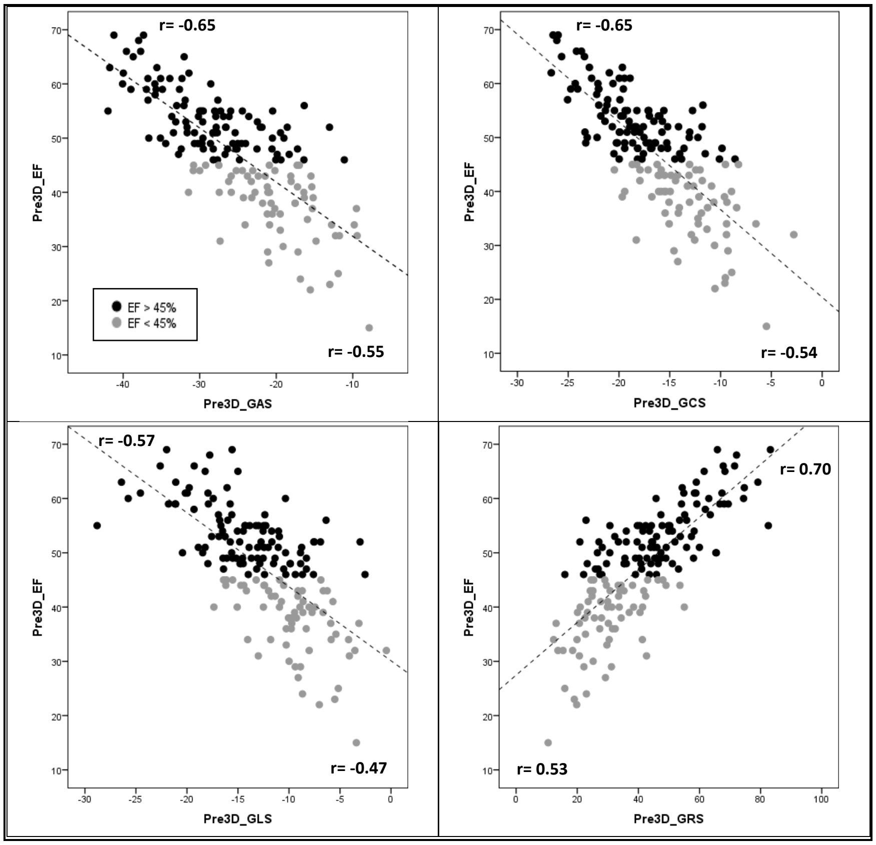
Appendix Figure 5. 3D EF and strain correlations: Pre-op measurements for patients with reduced pre-operative ventricular function (EF<45%)

		Post3D_EF	Post3D_GAS	Post3D_GCS	Post3D_GLS	Post3D_GRS	Post2D_EF	Post2D_GLPS	Post2D_GLCS	Post2D_Global_PS_Circ	Post2D_Global_PS_Radial
Post3D_EF	Pearson Correlation	1	-.676**	-.634**	-.466**	.678**	.461**	-.589**	-.188	-.197	.104
	N	59	59	59	59	59	59	59	59	59	59
Post3D_GAS	Pearson Correlation	-.676**	1	.830**	.777**	-.989**	-.362**	.690**	.295*	.297*	-.317*
Post3D_GCS	Pearson Correlation	-.634**	.830**	1	.306*	-.819**	-.302*	.566**	.201	.187	-.227
Post3D_GLS	Pearson Correlation	-.466**	.777**	.306*	1	-.779**	-.310*	.563**	.301*	.321*	-.289*
Post3D_GRS	Pearson Correlation	.678**	-.989**	-.819**	-.779**	1	.389**	-.705**	-.321*	-.325*	.354**
Post2D_EF	Pearson Correlation	.461**	-.362**	-.302*	-.310*	.389**	1	-.441**	-.347**	-.296*	.300*
Post2D_GLPS	Pearson Correlation	-.589**	.690**	.566**	.563**	-.705**	-.441**	1	.401**	.352**	-.352**
Post2D_GLCS	Pearson Correlation	-.188	.295*	.201	.301*	-.321*	-.347**	.401**	1	.926**	-.677**
Post2D_Global_PS_Circ	Pearson Correlation	-.197	.297*	.187	.321*	-.325*	-.296*	.352**	.926**	1	-.744**
Post2D_Global_PS_Radial	Pearson Correlation	.104	-.317*	-.227	-.289*	.354**	.300*	-.352**	-.677**	-.744**	1

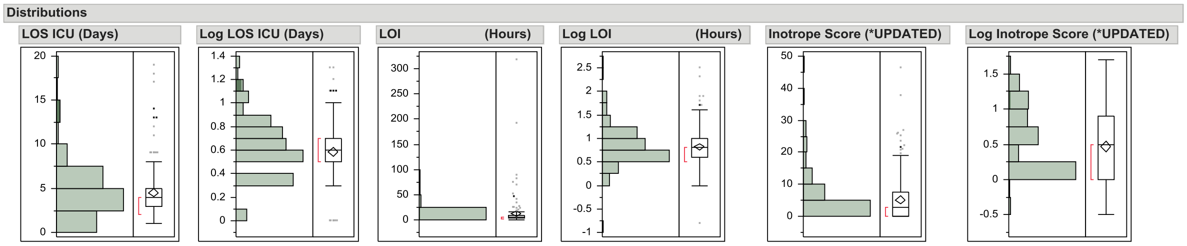
**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Appendix Figure 6. 3D EF and strain correlations: Post-op measurements for patients with reduced pre-operative ventricular function (EF<45%)



Appendix Figure 7. Scatterplots depicting correlation between pre-operative 3D ejection fraction (EF) and global strain, showing the reduction in correlation in patients with abnormal ventricular function, EF <45%. GAS =global Area strain, GLS=longitudinal strain, GCS=circumferential strain, GRS=radial strain.



Quantiles

		LOS ICU (Days)	Log LOS ICU (Days)	LOI (Hours)	Log LOI (Hours)	Inotrope Score (*UPDATED)	Log Inotrope Score (*UPDATED)
100.0	maximu	19	1.3	318.3	2.5	46.4	1.7
99.5%		19	1.3	318.3	2.5	46.4	1.7
97.5%		13.9	1.1	81.3	1.9	26.07	1.4
90.0%		8	0.9	19.4	1.3	14.42	1.16
75.0%	quartile	5	0.7	9.8	1	7.6	0.9
50.0%	median	4	0.6	5.7	0.8	3	0.5
25.0%	quartile	3	0.5	3.9	0.6	0	0
10.0%		2	0.3	2.54	0.4	0	0
2.5%		1	0	1.41	0.11	0	0
0.5%		1	0	0	-0.8	0	-0.5
0.0%	minimum	1	0	0	-0.8	0	-0.5

Summary Statistics

	LOS ICU (Days)	Log LOS ICU (Days)	LOI (Hours)	Log LOI (Hours)	Inotrope Score (*UPDATED)	Log Inotrope Score (*UPDATED)
Mean	4.4969325	0.5864198	12.709816	0.8196319	5.1871166	0.4625767
Std Dev	3.0253542	0.2505909	31.01395	0.4110899	7.5706234	0.4897828
Std Err Mean	0.236964	0.0196883	2.4292	0.032199	0.592977	0.0383627
Upper 95% Mea	4.9648691	0.6253003	17.506796	0.8832159	6.3580776	0.5383322
Lower 95% Mea	4.0289959	0.5475392	7.9128363	0.7560479	4.0161555	0.3868212
N	163	162	163	163	163	163

Appendix Figure 8. Histograms of outcome variable data distribution, showing improved spread of distribution with log transformation (LOG). LOS=length of stay, ICU=intensive care unit, LOI=length of intubation

References:

1. Ternacle J, Berry M, Alonso E, Kloeckner M, Couetil JP, Rande JL, Gueret P, Monin JL, Lim P. Incremental value of global longitudinal strain for predicting early outcome after cardiac surgery. *European heart journal cardiovascular Imaging*. 2013;14:77-84

2. Garcia-Bengochea JB, Fernandez AL, Calvelo DS, Escudero JA, Gude F, Juanatey JR. Temporary epicardial left ventricular and biventricular pacing improves cardiac output after cardiopulmonary bypass. *J Cardiothorac Surg*. 2012;7:113

3. Reynolds HR, Tunick PA, Grossi EA, Dilmanian H, Colvin SB, Kronzon I. Paradoxical septal motion after cardiac surgery: A review of 3,292 cases. *Clin Cardiol*. 2007;30:621-623

4. Jenkins C, Bricknell K, Chan J, Hanekom L, Marwick TH. Comparison of two- and three-dimensional echocardiography with sequential magnetic resonance imaging for evaluating left ventricular volume and ejection fraction over time in patients with healed myocardial infarction. *Am J Cardiol*. 2007;99:300-306

5. Kleijn SA, Brouwer WP, Aly MF, Russel IK, de Roest GJ, Beek AM, van Rossum AC, Kamp O. Comparison between three-dimensional speckle-tracking echocardiography and cardiac magnetic resonance imaging for quantification of left ventricular volumes and function. *European heart journal cardiovascular Imaging*. 2012;13:834-839

6. Thorstensen A, Dalen H, Hala P, Kiss G, D'Hooge J, Torp H, Stoylen A, Amundsen B. Three-dimensional echocardiography in the evaluation of global and regional function in patients with recent myocardial infarction: A comparison with magnetic resonance imaging. *Echocardiography*. 2013;30:682-692

7. Abate E, Hoogslag GE, Antoni ML, Nucifora G, Delgado V, Holman ER, Schalij MJ, Bax JJ, Marsan NA. Value of three-dimensional speckle-tracking longitudinal strain for predicting improvement of left ventricular function after acute myocardial infarction. *Am J Cardiol*. 2012;110:961-967

8. Luo XX, Fang F, Lee AP, Sun JP, Li S, Zhang ZH, Sanderson JE, Kwong JS, Zhang Q, Wang J, Yu CM. What can three-dimensional speckle-tracking echocardiography contribute to evaluate global left ventricular systolic performance in patients with heart failure? *Int J Cardiol*. 2014;172:132-137

9. Ciampi Q, Villari B. Role of echocardiography in diagnosis and risk stratification in heart failure with left ventricular systolic dysfunction. *Cardiovasc Ultrasound*. 2007;5:34

10. Hayat D, Kloeckner M, Nahum J, Ecochard-Dugelay E, Dubois-Rande JL, Jean-Francois D, Gueret P, Lim P. Comparison of real-time three-dimensional speckle tracking to magnetic resonance imaging in patients with coronary heart disease. *Am J Cardiol*. 2012;109:180-186

11. Matsumoto K, Tanaka H, Tatsumi K, Miyoshi T, Hiraishi M, Kaneko A, Tsuji T, Ryo K, Fukuda Y, Yoshida A, Kawai H, Hirata K. Left ventricular dyssynchrony using three-dimensional speckle-tracking imaging as a determinant of torsional mechanics in patients with idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2012;109:1197-1205

12. Nesser HJ, Mor-Avi V, Gorissen W, Weinert L, Steringer-Mascherbauer R, Niel J, Sugeng L, Lang RM. Quantification of left ventricular volumes using three-dimensional echocardiographic speckle tracking: Comparison with mri. *Eur Heart J*. 2009;30:1565-1573

13. Wen H, Liang Z, Zhao Y, Yang K. Feasibility of detecting early left ventricular systolic dysfunction using global area strain: A novel index derived from three-dimensional speckle-tracking echocardiography. *Eur J Echocardiogr*. 2011;12:910-916

14. Macron L, Lairez O, Nahum J, Berry M, Deal L, Deux JF, Bensaid A, Dubois Rande JL, Gueret P, Lim P. Impact of acoustic window on accuracy of longitudinal global strain: A comparison study to cardiac magnetic resonance. *Eur J Echocardiogr*. 2011;12:394-399

15. Meunier J. Tissue motion assessment from 3d echographic speckle tracking. *Physics in medicine and biology*. 1998;43:1241-1254

16. Nashef SA, Roques F, Hammill BG, Peterson ED, Michel P, Grover FL, Wyse RK, Ferguson TB. Validation of european system for cardiac operative risk evaluation (euroscore) in north american cardiac surgery. *Eur J Cardiothorac Surg*. 2002;22:101-105

17. Wernovsky G, Wypij D, Jonas RA, Mayer JE, Jr., Hanley FL, Hickey PR, Walsh AZ, Chang AC, Castaneda AR, Newburger JW, et al. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation*. 1995;92:2226-2235

18. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, Charpie JR, Hirsch JC. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med*. 2010;11:234-238

19. Soliman OI, Kirschbaum SW, van Dalen BM, van der Zwaan HB, Delavary BM, Vletter WB, van Geuns RJ, Ten Cate FJ, Geleijnse ML. Accuracy and reproducibility of quantitation of left ventricular function by real-time three-dimensional echocardiography versus cardiac magnetic resonance. *Am J Cardiol*. 2008;102:778-783

20. Udelson JE, Feldman AM, Greenberg B, Pitt B, Mukherjee R, Solomon HA, Konstam MA. Randomized, double-blind, multicenter, placebo-controlled study evaluating the effect of aldosterone antagonism with eplerenone on ventricular remodeling in patients with mild-to-moderate heart failure and left ventricular systolic dysfunction. *Circulation. Heart failure*. 2010;3:347-353

21. Dokainish H, Rajaram M, Prabhakaran D, Afzal R, Orlandini A, Staszewsky L, Franzosi MG, Llanos J, Martinoli E, Roy A, Yusuf S, Mehta S, Lonn E. Incremental value of left ventricular systolic and diastolic function to determine outcome in patients with acute st-segment elevation myocardial infarction: The echocardiographic substudy of the oasis-6 trial. *Echocardiography*. 2013

22. Luis SA, Yamada A, Khandheria BK, Speranza V, Benjamin A, Ischenko M, Platts DG, Hamilton-Craig CR, Haseler L, Burstow D, Chan J. Use of three-dimensional speckle-tracking echocardiography for quantitative assessment of global left ventricular function: A comparative study to three-dimensional echocardiography. *J Am Soc Echocardiogr*. 2014;27:285-291

23. Ammar KA, Paterick TE, Khandheria BK, Jan MF, Kramer C, Umland MM, Tercius AJ, Baratta L, Tajik AJ. Myocardial mechanics: Understanding and applying three-dimensional speckle tracking echocardiography in clinical practice. *Echocardiography*. 2012;29:861-872

24. Saito K, Okura H, Watanabe N, Hayashida A, Obase K, Imai K, Maehama T, Kawamoto T, Neishi Y, Yoshida K. Comprehensive evaluation of left ventricular strain using speckle tracking echocardiography in normal adults: Comparison of three-dimensional and two-dimensional approaches. *J Am Soc Echocardiogr*. 2009;22:1025-1030

25. Rost C, Korder S, Wasmeier G, Wu M, Klinghammer L, Flachskampf FA, Daniel WG, Voigt JU. Sequential changes in myocardial function after valve replacement for aortic stenosis by speckle tracking echocardiography. *Eur J Echocardiogr*. 2010;11:584-589

26. Enriquez-Sarano M, Tajik AJ, Schaff HV, Orszulak TA, McGoon MD, Bailey KR, Frye RL. Echocardiographic prediction of left ventricular function after correction of mitral regurgitation: Results and clinical implications. *J Am Coll Cardiol*. 1994;24:1536-1543

27. Carasso S, Cohen O, Mutlak D, Adler Z, Lessick J, Aronson D, Reisner SA, Rakowski H, Bolotin G, Agmon Y. Relation of myocardial mechanics in severe aortic stenosis to left ventricular ejection fraction and response to aortic valve replacement. *Am J Cardiol*. 2011;107:1052-1057

28. Kleijn SA, Aly MF, Terwee CB, van Rossum AC, Kamp O. Three-dimensional speckle tracking echocardiography for automatic assessment of global and regional left ventricular function based on area strain. *J Am Soc Echocardiogr*. 2011;24:314-321

29. Vaskelyte J, Stoskute N, Kinduris S, Ereminiene E. Coronary artery bypass grafting in patients with severe left ventricular dysfunction: Predictive significance of left ventricular diastolic filling pattern. *Eur J Echocardiogr*. 2001;2:62-67