Original Article

Post-Cardiopulmonary Bypass Longitudinal Strain provides Higher Prognostic Ability than Baseline Strain or Change in Strain

Brett J. Wakefield, Amanda S. Artis[1], Andrej Alfirevic[2], Shiva Sale[2], Andra E. Duncan[2]

Departments of Intensive Care and Resuscitation, Cardiothoracic Anesthesiology, and Quantitative Health Sciences, [1]Quantitative Health Sciences, [2]Cardiothoracic Anesthesiology, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH, USA

ABSTRACT

Context: Global longitudinal strain (GLS) measured by speckle-tracking echocardiography demonstrates excellent prognostic ability in predicting major adverse cardiac events after cardiac surgery. However, the optimal timing of intraoperative GLS measurement that provides the best prognostic value is unclear.

Aim: Our goal was to evaluate whether GLS measured prior to cardiopulmonary bypass (pre-CPB GLS), following CPB (post-CPB GLS), or change in GLS provides the strongest association with postoperative complications.

Setting and Design: *Post hoc* analysis of prospectively collected data from a clinical trial (NCT01187329). 72 patients with aortic stenosis undergoing elective AVR ± coronary artery bypass grafting between January 2011 and August 2013.

Material and Methods: Myocardial deformation analysis from standardized transesophageal echocardiographic examinations were performed after anesthetic induction and chest closure. We evaluated the association between pre-CPB GLS, post-CPB GLS, and change in GLS (percent change from pre-CPB baseline) with postoperative atrial fibrillation and hospitalization >7 days. The association of post-CPB GLS with duration of mechanical ventilation, N-terminal pro-BNP (NT-proBNP) and troponin T were also assessed.

Statistical Analysis: Multivariable logistic regression.

Results: Risk-adjusted odds (OR[97.5%CI] of prolonged hospitalization increased an estimated 27% (1.27[1.01 to 1.59];P_{adj}=0.035) per 1% decrease in absolute post-CPB GLS. Mean[98.3%CI] NT-proBNP increased 98.4[20 to 177]pg/mL; P_{adj}=0.008), per 1% decrease in post-CPB GLS. Pre-CPB GLS or change in GLS were not associated with any outcomes.

Conclusions: Post-CPB GLS provides the best prognostic value in predicting postoperative outcomes. Measuring post-CPB GLS may improve risk stratification and assist in future study design and patient outcome research.

Keywords: Aortic valve replacement, atrial fibrillation, global longitudinal strain, myocardial deformation, prolonged hospitalization, transesophageal echocardiography

Address for correspondence: Dr. Andra E. Duncan, Cardiothoracic Anesthesiology, Cleveland Clinic, 9500 Euclid Avenue, J4-331, Cleveland, OH - 44195, USA.
E-mail: duncana@ccf.org

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INTRODUCTION

Global longitudinal strain (GLS) measured by speckle-tracking echocardiography demonstrates excellent prognostic ability in predicting major adverse cardiac events[1] and mortality[2] following cardiac surgery. However, intraoperative use of GLS remains limited, perhaps in part,

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because the optimal timing of GLS measurement that provides the best prognostic value is unclear.

Reduced GLS measured by transesophageal echocardiography (TEE) prior to cardiopulmonary bypass (*pre-CPB*) is associated with worse postoperative outcomes, including prolonged hospitalization following aortic valve replacement (AVR).[3] Pre-CPB GLS, however, does not reflect adverse intraoperative events, including inadequate myocardial protection, prolonged aortic cross-clamp time, ischemia-reperfusion injury, or surgical complications, which increase the risk of myocardial dysfunction following cardiac surgery.[4,5] Measuring *post-CPB* GLS may thus better predict outcomes after cardiac surgery.

Alternatively, *the intraoperative change in GLS* may provide superior prognostic value and better predict postoperative outcomes – specifically after AVR, because an early improvement in myocardial function predicts favorable functional outcomes and better survival after AVR. For example, patients whose left ventricular ejection fraction improves by 10% after AVR experience significantly improved New York Heart Association heart failure functional class and longer survival.[6] One explanation is that higher LV function after AVR suggests reversible myocardial disease, while no change or worse LV function suggests an irreversible myocardial pathologic process and worse outcomes.[2,7] Thus, assessing the intraoperative change in GLS between pre- and post-CPB may provide better prognostic value than pre-CPB GLS. Determining the optimal timing (pre- versus post-CPB) or whether change in GLS provides the best prognostic value will improve perioperative risk stratification and guide future research in postoperative outcomes.

GLS is associated with other predictive biomarkers including postoperative N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels, as well as clinical signs of myocardial insufficiency, heart failure, and inotropic and vasopressor requirements in cardiac surgical patients.[8,9] Considering that laboratory markers, including postoperative brain natriuretic peptide (BNP) and troponin T concentrations, reflect myocardial performance and predict major adverse cardiac events, postoperative atrial fibrillation, and 1-year mortality,[10,11] we examined whether worse post-CPB GLS was associated with increased serum NT-proBNP, troponin T concentrations, and other clinical outcomes.

The primary aim of this investigation was to determine the optimal timing and assessment of GLS that provides the greatest predictive value after cardiac surgery. We compared whether post-CPB GLS and the change in GLS (ΔGLS%) were better predictors than pre-CPB GLS for postoperative complications, including atrial fibrillation and prolonged hospitalization (>7 days) following AVR. We also evaluated the association between post-CPB GLS and postoperative laboratory measures, including NT-proBNP and troponin T concentrations, and duration of mechanical ventilation after cardiac surgery. We hypothesized that *post-CPB GLS provides the strongest prognostic value for postoperative complications* in patients with aortic stenosis having AVR.

MATERIALS AND METHODS

This investigation is a supplementary analysis of data from a prospective randomized clinical trial, "Effect of hyperinsulinemic normoglycemia on myocardial function and utilization of glucose," (ClinicalTrials.gov#NCT01187329).[12] This investigation was approved by the Institutional Review Board with waived consent. Each participant provided written consent for inclusion in the primary study. We previously reported that pre-CPB strain predicts postoperative outcomes.[3] This report extends our results by determining whether alternative measures of intraoperative myocardial function (post-CPB GLS, ΔGLS%) provide superior prognostic ability compared with pre-CPB for postoperative outcomes. This report follows guidelines reported by STrengthening the Reporting of OBservational studies in Epidemiology (STROBE).

Selection and description of participants

We included adult patients aged 40-84 with severe aortic stenosis presenting for elective AVR with or without coronary artery bypass graft surgery (CABG) between January 2011 to August 2013. Participants with aortic regurgitation without aortic stenosis, required hypothermic circulatory arrest, had contraindications to TEE, or poor echocardiographic images (>3 unacceptable myocardial segments in speckle-tracking echocardiographic analysis) were excluded. Of 100 patients enrolled in the primary clinical trial, 72 had acceptable pre- and post-CPB GLS measurements enabling investigation of our primary and secondary outcomes [Figure 1]. Considering the primary clinical trial revealed no difference in the primary outcome of GLS between groups, both randomized groups were combined for this analysis.

Anesthesia and surgery

Anesthetic and surgical management were previously described.[12] Following separation from CPB, epinephrine and/or milrinone were administered when the cardiac

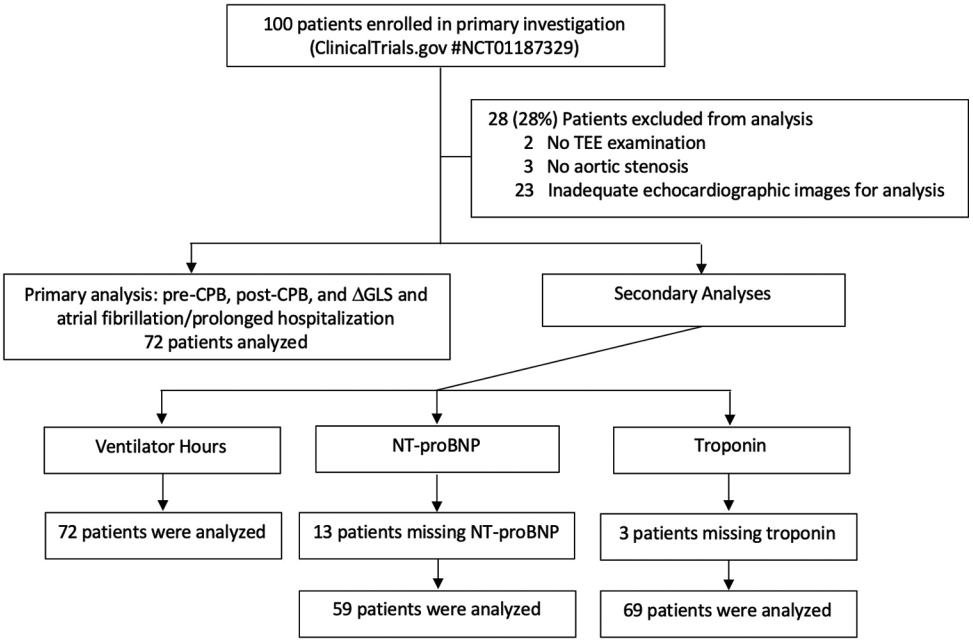

Figure 1: Types and numbers of exclusions for the available subjects within our previously randomized clinical trial and considered for this current analysis. (21/40 words). TEE = transesophageal echocardiography. NT-proBNP = N-terminal prohormone of brain natriuretic peptide

index ≤2.0 L/min/m^2 despite adequate intravascular volume replacement. Norepinephrine was initiated when cardiac index was ≥2.0 L/min/m^2 with a systolic blood pressure below 90 mmHg or systemic vascular resistance <800 dynes-s/cm^5.

Echocardiographic assessment

A standardized investigative TEE examination was performed by one of three cardiothoracic anesthesiologists Board-certified by the National Board of Echocardiography following induction of anesthesia (prior to surgical incision) and following sternal closure. Images were stored for off-line analysis as previously described.[12]

TEE images for the assessment of GLS were captured from the midesophageal level at transducer angles of 0°, 60°, and 120°, corresponding to four-chamber, mitral commissural, and long axis views, respectively. The original clinical trial was among the first investigations to use TEE to evaluate myocardial strain. This analysis was thus performed prior to current recommendations or software suggesting the use of the four-chamber, two-chamber, and long-axis views. Transducer angles of 0°, 60°, and 120° were selected in order to capture equally divided segments of the myocardium. If temporary epicardial pacing was required post-CPB, pacing was temporarily discontinued for echocardiographic strain measurements. GLS was calculated off-line using speckle-tracking echocardiography software (EchoPAC v. 112; GE Healthcare Vingmed Ultrasound AS, Horten, Norway).[12] GLS was calculated as the average of six myocardial segments from three echocardiographic views for a total of 18 myocardial segments. Patients were included in the analysis if 15 of 18 segments were deemed acceptable by the investigator.[12] Off-line strain analysis was performed by a single cardiothoracic anesthesiologist (AED).

Exposures of interest

Pre-CPB GLS – peak systolic global longitudinal strain measured after anesthesia induction prior to surgical incision.

Post-CPB GLS – peak systolic global longitudinal strain measured at end of surgery following chest closure.

Change in strain (ΔGLS%) – the change in GLS between beginning (after induction and before incision; T1) and end (after chest closure; T2) of surgery. ΔGLS% is calculated utilizing the formula from Hu *et al.*[7]:

$$\Delta GLS\% = \frac{GLS_{T1} - GLS_{T2}}{GLS_{T1}} \times 100\%$$

According to this formula, an improvement in strain following CPB for AVR is represented by a negative ΔGLS% while worsening strain is represented by a positive ΔGLS%.

Outcome measures

Prolonged hospitalization – hospital stay greater than 7 days following AVR, indicating a more complicated recovery.

New-onset atrial fibrillation – postoperative occurrence of atrial fibrillation requiring treatment (antiarrhythmic therapy, rate-control therapy, cardioversion) without prior history of atrial fibrillation.

Duration of mechanical ventilation – the duration of time (hours) between ICU arrival and tracheal extubation.

Serum troponin T – measured at approximately 2:00AM on the first postoperative day.

NT-proBNP – measured 24 hours after surgery.

Statistical methods

Primary analysis

We examined associations between pre-CPB and post-CPB GLS and the clinical outcomes, postoperative atrial fibrillation and prolonged hospitalization (>7 days), via multivariable logistic regression with adjustment for randomization treatment, age, duration of cardiopulmonary bypass, and surgical procedure (AVR versus AVR with concomitant CABG). We adjusted for presence of CABG and the treatment effect from hyperinsulinemic normoglycemia in the regression model because of a possible confounding effect of these variables.

Covariate adjusted odd ratios (ORs) for postoperative atrial fibrillation and prolonged hospitalization per 1% decrease in absolute GLS are reported, along with Bonferroni-corrected 98.75% confidence intervals (CIs). Corresponding Bonferroni-corrected *P* values (P_{adj}) to adjust for testing two hypotheses are also reported. These adjusted *P* values are equivalent to the raw *P* value times the number of tests performed to control for the inflated type I error rate. This enables direct comparison of all reported P_{adj} to $\alpha = 0.05$ for significance testing.

Secondarily, the relationship between ΔGLS% and clinical outcomes atrial fibrillation and prolonged hospitalization were assessed and presented utilizing the methods outlined above. Covariate adjusted ORs for ΔGLS% are reported with Bonferroni-corrected 97.5%CIs. An increase in ΔGLS% represents a worsening in myocardial function.

Assessment of GLS with NT-proBNP, troponin T, and duration of mechanical ventilation

We explored the relationship between post-CPB GLS and three outcomes – NT-proBNP, duration of mechanical ventilation, and troponin T concentrations– using multivariable gamma regression modeling. The identity link was used for NT-proBNP; the log link was used for duration of mechanical ventilation and troponin. Two observations were excluded from the mechanical ventilation analysis due to high influence. Preoperative NT-proBNP was added to the model for the postoperative NT-proBNP outcome. Estimated mean change in LOS per 1% increase in GLS with corresponding 98.3% Wald CIs and P_{adj} are presented.

Power analysis

We included all available patients from our clinical trial.[12] Power was estimated using a univariable logistic regression model (i.e. without covariables) assuming that GLS is normally distributed with a mean (standard deviation, SD) of -17 (4)% and using the observed incidence of 35% and 26% for atrial fibrillation and prolonged hospitalization, respectively. With 72 patients in the primary analyses and a Bonferroni-adjusted $\alpha = 0.025$, we estimate that we would have sufficient power (>90%) to detect an odds ratio for a 1% unit decrease in GLS of 1.30 or more for postoperative atrial fibrillation and 1.32 or more for prolonged hospitalization.

For ΔGLS%, we used the conservative estimates reported in Hu *et al.*[7] and assumed ΔGLS% is normally distributed with a mean (SD) of 15.3 (2.0) and the same observed incidences for atrial fibrillation and prolonged hospitalization. With 72 patients and a Bonferroni-adjusted $\alpha = 0.025$, we estimate that we would have sufficient power (>90%) to detect an odds ratio for a unit increase in ΔGLS% of 1.66 or more for postoperative atrial fibrillation and 1.71 or more for prolonged hospitalization.

RESULTS

Of N = 100 subjects enrolled in the clinical trial, N = 72 patients had post-CPB echocardiographic images with at least 5 of 6 acceptable myocardial segments. These same N = 72 subjects also had acceptable pre-CPB data, enabling examination of ΔGLS%. For descriptive purposes, post-CPB GLS was broken into three approximately equal tertiles in Table 1 for examination of patient characteristics, perioperative, echocardiographic variables, and postoperative complications. Of note, atrial fibrillation was not present in any patients during strain measurement.

Primary analysis

Neither Pre-CPB (OR[98.75%CI]: 1.04 [0.87to1.26] per 1% worsening of GLS; $P_{adj} > 0.99$) nor post-CPB GLS (0.94[0.79to1.13] per 1% unit decrease in GLS; $P_{adj} > .99$) were associated with postoperative atrial fibrillation. Pre-CPB was not associated with odds of prolonged hospitalization (1.21[0.98 to1.50], $P_{adj} = 0.10$; please note a slight difference from our previous report[3] due to Bonferroni correction for four, rather than 3,

Table 1: Patient demographics, co-morbidities, and perioperative variables shown in Total and by Tertile of post-cardiopulmonary (post-CPB) Global Longitudinal Strain (GLS)

Variable	Total	Post-CPB GLS Tertile			*P*
		1st	2nd	3rd	
	(*n*=72)	(*n*=24)	(*n*=24)	(*n*=24)	
GLS					
Post-CBP GLS, %	16.3±4.6	21.0±1.9	17.1±1.5	10.9±2.1	<.001[a]
ΔGLS*, %	3.7±19.0	-5.1±13.2	-0.43±12.9	16.5±22.5	<.001[a]
Demographics					
Age, years	69.0±9.3	71.5±8.9	69.1±7.3	66.3±10.8	0.14[a]
Sex, female	24 (33.3)	9 (37.5)	9 (37.5)	6 (25.0)	0.57[c]
BMI, kg/m^2	31.2±7.8	30.2±9.3	31.3±7.5	32.1±6.5	0.72[a]
Medical History					
Hypertension	16 (22.2)	4 (16.7)	5 (20.8)	7 (29.2)	0.57[c]
Diabetes	22 (30.6)	5 (20.8)	8 (33.3)	9 (37.5)	0.43[c]
Congestive Heart Failure	11 (15.3)	2 (8.3)	3 (12.5)	6 (25.0)	0.35[d]
Myocardial Infarction	6 (8.3)	0 (0.0)	0 (0.0)	6 (25.0)	0.003[d]
Pulmonary Hypertension	13 (18.1)	2 (8.3)	4 (16.7)	7 (29.2)	0.20[d]
Stroke	3 (4.2)	1 (4.2)	1 (4.2)	1 (4.2)	0.99[d]
Peripheral Vascular Disease	7 (9.7)	3 (12.5)	0 (0.0)	4 (16.7)	0.15[d]
Previous Vascular Surgery	3 (4.2)	1 (4.2)	0 (0.0)	2 (8.3)	0.77[d]
Preoperative NT-proBNP†	287.0 [139.0, 627.0]	160.0 [92.0, 432.0]	445.5 [168.5, 689.5]	418.0 [223.0, 1574.0]	0.021[b]
Surgical Characteristics					
Re-operative Cardiac Surgery	18 (25.0)	0 (0.0)	5 (20.8)	13 (54.2)	<.001[c]
Duration of surgery, min	372.5 [315.5, 435.0]	320.5 [285.0, 371.0]	347.5 [320.0, 413.0]	443.0 [384.0, 487.0]	<.001[b]
Cardiopulmonary Bypass Time, min	86.0 [67.0, 118.5]	74.5 [56.0, 86.0]	81.0 [60.5, 103.0]	118.0 [94.0, 129.5]	<.001[b]
Aortic Cross Clamp Time, min	64.0 [49.5, 81.0]	58.5 [46.0, 69.0]	57.5 [47.5, 82.5]	73.0 [65.0, 98.0]	0.009[b]
Concomitant CABG	31 (43.1)	9 (37.5)	8 (33.3)	14 (58.3)	0.17[c]
Aortic Insufficiency ≥1+	44 (62.0)	15 (62.5)	17 (70.8)	12 (52.2)	0.81[b]
Vasoactive Infusions					0.001[c]
Epinephrine	12 (16.7)	0 (0.0)	2 (8.3)	10 (47.8)	
Norepinephrine	19 (26.4)	6 (25.0)	8 (33.3)	5 (20.8)	
Neither	41 (56.9)	18 (75.0)	14 (58.3)	9 (37.5)	
Post-surgical Outcomes					
1-Year Mortality	2 (2.8)	0 (0.0)	1 (4.2)	1 (4.2)	0.99[d]
30-Day Readmission*	11 (17.5)	1 (4.5)	5 (23.8)	5 (25.0)	0.13[d]

Statistics presented as Mean±SD, Median [IQR], or N (column %). *A negative number represents an improvement in cardiac function from pre-CBP values. †Data not available for all subjects. Missing values: Preoperative NT-proBNP=11, Degree of Aortic Insufficiency=1, 30-Day Readmission=9. *P*-values: a=ANOVA, b=Kruskal-Wallis test, c=Pearson's chi-square test, d=Fisher's Exact test. GLS=global longitudinal strain, Post-CPB=Post-cardiopulmonary bypass, BMI=body mass index, NT-proBNP=N-terminal prohormone of brain natriuretic peptide, CABG=Coronary artery bypass graft, HNC=Hyperinsulinemic Normoglycemic Clamp, IQR=interquartile range

outcomes). However, odds of prolonged hospitalization increased an estimated 27% (1.27[1.01to1.59]P_{adj}=0.035) per 1% decrease in absolute post-CPB GLS, after adjusting for predefined confounders. A summary of regression results and OR forest plots are presented in Table 2 and Figure 1.

We found no association between ΔGLS% and postoperative atrial fibrillation (OR[97.5%CI]:0.97[0.93to1.01] per unit increase in ΔGLS%, P_{adj}=0.22) or prolonged hospitalization (OR[97.5%CI]:1.02[0.98to1.06] per unit increase in ΔGLS%, P_{adj}=0.68) [Table 2, Figure 2].

Secondary analysis

Mean NT-proBNP increased an estimated 98 pg/mL (98.3%CI [20 to177]pg/mL, P_{adj}=0.008) per 1% decrease in post-CPB GLS [Figure 3]. However, there was no association between GLS and duration of mechanical ventilation (estimated mean increase [98.3%CI]:1.03[0.97to1.10] times per 1% increase in GLS, P_{adj}=0.52). There was no association between GLS and troponin (estimated mean increase [98.3%CI]:1.04[0.98to1.10] ng/mL times per 1% increase in GLS, P_{adj}=.32).

DISCUSSION

Our investigation examined the association between pre-CPB and post-CPB GLS and postoperative outcomes and found the predictive value of post-CPB GLS on prolonged hospitalization was modestly stronger. For every unit worsening in post-CPB GLS, the odds of prolonged hospitalization increased by 27%, demonstrating higher odds than pre-CPB GLS. In contrast, the change in GLS from pre- to post-CPB was not predictive of either outcome. Furthermore, each 1% worsening of post-CPB GLS increased NT-proBNP concentrations by nearly 100 pg/mL. Therefore post-CPB GLS provided the most

Table 2: Summary of multivariable logistic and multivariable log-linear regression results investigating the relationship between myocardial deformation and postoperative morbidity. Raw data is shown in Total and by Tertile of post-cardiopulmonary (post-CPB) Global Longitudinal Strain (GLS). Adjusted Odds ratios and confidence intervals are shown. Values are presented as *n* (column %) or Median [IQR]

Exposure	Total	Post-CPB GLS Tertiles			Estimate (CI)	P_{adj}
		1st	2nd	3rd		
	(*n*=72)	(*n*=24)	(*n*=24)	(*n*=24)		
Pre-CPB GLS (%)*					OR (98.75% CI)	
Atrial Fibrillation	25 (34.7)	8 (33.3)	9 (37.5)	8 (33.3)	1.04 (0.87 to 1.26)	>0.99
Hospitalization (>7 days)	18 (25.0)	5 (20.8)	3 (12.5)	10 (41.7)	1.21 (0.98 to 1.50)	0.10
Post-CPB GLS (%)*					OR (97.5% CI)	
Atrial Fibrillation	25 (34.7)	8 (33.3)	9 (37.5)	8 (33.3)	0.94 (0.79 to 1.13)	>0.99
Hospitalization (>7 days)	18 (25.0)	5 (20.8)	3 (12.5)	10 (41.7)	1.27 (1.01 to 1.59)	0.035
ΔGLS%†					OR (97.5% CI)	
Atrial Fibrillation	25 (34.7)	8 (33.3)	9 (37.5)	8 (33.3)	0.97 (0.93 to 1.01)	0.225
Hospitalization (>7 days)	18 (25.0)	5 (20.8)	3 (12.5)	10 (41.7)	1.02 (0.98 to 1.06)	0.677
Post-CPB GLS (%)‡					Mean Change (98.3% CI)§	
NT-proBNP*	2194.3±1781.3	1672.9±1380.9	2087.6±1276.1	2762.5±2326.4	98.4 (19.9 to 176.9)	0.008
Duration of Mechanical Ventilation, hours	4.0 [3.0, 7.0]	4.0 [3.0, 5.5]	4.0 [3.0, 7.0]	5.0 [4.0, 14.5]	3% (-3% to 10%)	0.523
Troponin*	0.45 [0.18, 0.79]	0.35 [0.15, 0.73]	0.38 [0.19, 0.54]	0.62 [0.38, 1.05]	4% (-2% to 10%)	0.323

Postoperative GLS is presented in tertiles for the sole purpose of summarizing the raw, unadjusted relationships between GLS and our outcomes. All primary and tertiary analyses used continuous GLS in the regression models; continuous ΔGLS% as was used in the secondary analyses. Thus all estimates should be interpreted as estimated change in the outcome per 1% increase in GLS or ΔGLS (respective exposures are italicized). *Primary analyses: Multivariable logistic regression OR (97.5% CIs), adjusted for randomization treatment, age, duration of cardiopulmonary bypass, and concomitant CABG, and Bonferroni-corrected *P* values are presented for the relationship between postoperative GLS and two outcomes – postoperative atrial fibrillation and prolonged hospitalization. †Secondary analyses: Multivariable logistic regression OR (97.5% CIs), adjusted for randomization treatment, age, duration of cardiopulmonary bypass, and concomitant CABG, and Bonferroni-corrected *P* values are presented for the relationship between ΔGLS% and two outcomes – postoperative atrial fibrillation and prolonged hospitalization. ‡Tertiary analyses: Multivariable gamma regression Mean Change (98.3% CIs), adjusted for randomization treatment, age, duration of cardiopulmonary bypass, and concomitant CABG, and Bonferroni-corrected *P* values are presented for the relationship between postoperative value GLS and three outcomes – NT-proBNP, duration of mechanical ventilation, and troponin. Preoperative NT-proBNP was also included in the model for the post-CPB NT-proBNP outcome. §Estimate for NT-proBNP is mean change per 1% decrease in absolute GLS; Estimates for duration of mechanical ventilation and troponin are percent changes per 1% decrease in absolute GLS. ΔGLS% = [(Preoperative GLS – Postoperative GLS)/Preoperative GLS] × 100. Post-CPB=Post-cardiopulmonary bypass, GLS=global longitudinal strain, OR=odds ratio, CI=confidence interval, Padj=Bonferroni corrected P values, IQR=interquartile range, NT pro-BNP=N-terminal prohormone of brain natriuretic peptide, CABG=Coronary artery bypass graft

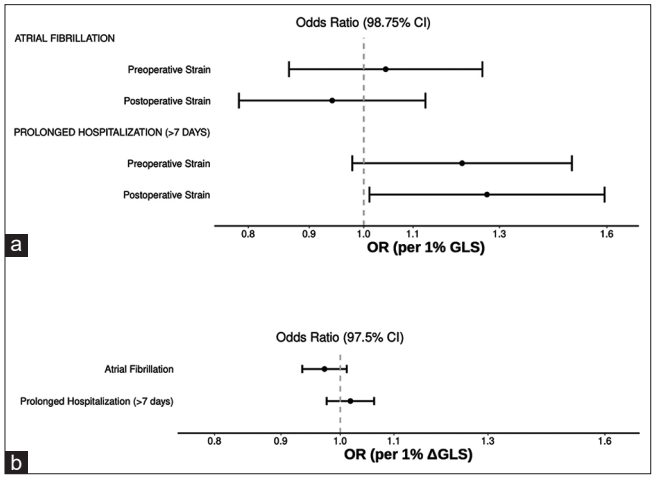

Figure 2: Covariable-adjusted OR forest plots for the relationship between preoperative and postoperative GLS (a), change in strain (ΔGLS%, b) and postoperative atrial fibrillation and prolonged hospitalization. Multivariable logistic regression OR adjusted for randomization treatment, age, CPB duration, and concomitant CABG. Bonferroni-corrected *P* values are presented. (40/40 words). OR = odds ratio, CI = confidence interval, CABG = Coronary artery bypass grafting, GLS = global longitudinal strain, ΔGLS% = [(Preoperative GLS – Postoperative GLS)/Preoperative GLS] × 100; CPB = cardiopulmonary bypass

useful measurement of intraoperative myocardial function. This result will influence future study design and guide research on postoperative outcomes.

Our results confirm that GLS is predictive of postoperative complications. Importantly, post-CPB represents the optimal time to assess LV function using GLS. We expected that post-CPB GLS would better predict morbidity following AVR than pre-CPB GLS because it more accurately reflects post-CPB hemodynamics, specifically reduced afterload following removal of a stenotic valve, as well as myocardial recovery after cardioplegic arrest, surgical complications or any intraoperative adverse events. Certainly, our results demonstrated that patients with the worst post-CPB GLS (categorized in the third post-CPB GLS tertile) had increased surgical duration, CPB time, and aortic cross-clamp time than the first and second tertiles of post-CPB GLS suggesting that post-CPB GLS best reflects intraoperative events. Post-CPB GLS would likely have demonstrated an even stronger association if the incidence of inadequate myocardial protection or surgical complications were higher in our study population. The

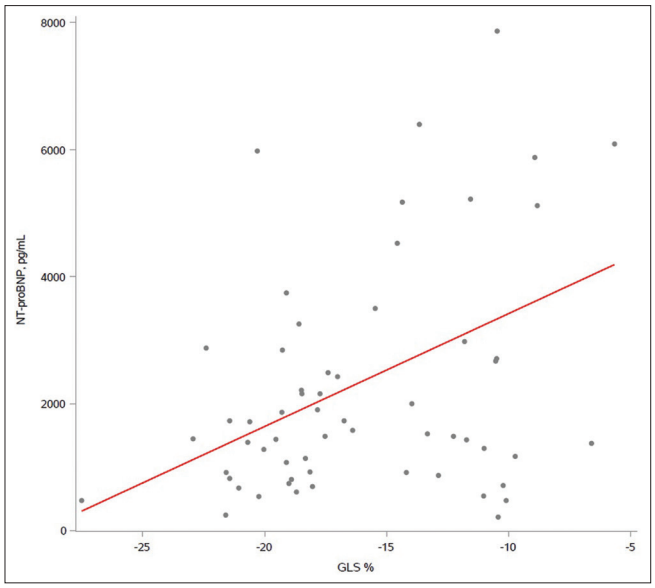

Figure 3: Scatterplot of Post-CPB GLS vs. NT-proBNP. Multivariable gamma regression using the identity link and adjusting for treatment, age, CPB duration, concomitant CABG, and preoperative NT-proBNP was used to assess the relationship between post-CPB GLS and NT-proBNP. GLS = Global Longitudinal Strain; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; Post-CPB = Post-cardiopulmonary bypass; CPB = cardiopulmonary bypass; CABG = coronary artery bypass grafting

incidence of norepinephrine or epinephrine requirement was higher in patients with worse post-CPB GLS. Because inotropic support would be expected to improve GLS due to increased contraction of the myocardial longitudinal fibers, these patients may have exhibited even worse GLS values without inotropic support.

Change in strain (ΔGLS%) was not associated with any postoperative complications. Others demonstrated an improvement in strain immediately following transcatheter aortic valve replacements.[13] Similarly, strain improves following surgical AVR documented at one week to 15 months following the procedure.[14,15] In the present study, patients with the most improved myocardial function, categorized in the first post-CPB GLS tertile, experienced a mean improvement in strain by approximately 5% (absolute value) compared with patients in the third tertile, who demonstrated a mean reduction of strain by 16.5%. However, the incidence of postoperative complications was no different depending on change in strain. Because our calculation for change in strain did not consider radial or circumferential strain, these dimensions may have compensated for a decrease in longitudinal strain. While this limitation may help explain the lack of association between the change in strain and prolonged hospitalization, we previously found that global radial or circumferential strain were not strongly associated with adverse outcomes.[16] Therefore, absolute post-CBP GLS, rather than the relative change in GLS, appears to be a better predictor of postoperative outcomes. The association between post-GLS or change in GLS with long-term postoperative outcomes including 1-year mortality or 30-day readmission rates could not be examined because these events were rare.

Neither post-CPB GLS nor Δ GLS% predicted the development of new-onset postoperative atrial fibrillation. In fact, the incidence of atrial fibrillation was almost identical across all tertiles of GLS, with an odds ratio approaching 1.0. Preoperative myocardial dysfunction is a known predictor of atrial fibrillation,[17] and in contrast to the present investigation, studies have reported associations between preoperative and post-CPB strain as well as Δ GLS% as predictors of atrial fibrillation.[7] Atrial fibrillation is known to be associated with postoperative left ventricular dysfunction,[7] increased atrial pressure and acute atrial stretch,[18] and prolonged aortic cross-clamp times.[19] Therefore the incidence of atrial fibrillation may increase following AVR in patients with reduced myocardial contractility and increased filling pressures. Considering there is a similar incidence of atrial fibrillation between on-pump and off-pump CABG,[20] CPB may not affect the development of atrial fibrillation; however inadequate atrial silence during cardioplegic arrest may lead to ischemia and atrial fibrillation.[21] While these factors suggest decreased post-CPB myocardial function may increase the risk of atrial fibrillation, inotrope usage immediately following separation from CPB will increase GLS but may also increase the risk of atrial fibrillation.[22] Despite this information, the exact etiology of postoperative atrial fibrillation has not been elucidated and our report finds no evidence that myocardial strain can predict the occurrence of atrial fibrillation.[23]

In our investigation, we found no association between the duration of mechanical ventilation and post-CPB GLS. Given reduced cardiac function is a known risk factor for prolonged ventilation following cardiac surgery, we expected to find an association between post-CPB GLS and duration of mechanical ventilation.[24] However, this retrospective analysis did not standardize the process of weaning from mechanical ventilation, so variation in provider techniques may explain the lack of association. Further, most patients were weaned within a few hours after surgery, making it challenging to discriminate the duration of mechanical ventilation by differences in GLS.

Decreased post-CPB GLS was associated with higher postoperative NT-proBNP values. Certainly, NT-proBNP concentrations have been shown to correlate with GLS

likely due to increased wall tension and pressure load in the ventricle as myocardial function falls.[25] Postoperative elevated NT-proBNP concentrations are associated with prolonged aortic cross-clamp time, the use of vasopressors, and postoperative cardiac dysfunction.[26,27] Furthermore, increased NT-proBNP levels predict a poor prognosis in heart failure, valvular disease, and coronary artery disease, and NT-proBNP levels are known to increase with the severity of aortic stenosis.[28] Our results provide evidence that NT-proBNP increases with falling GLS after surgical AVR.

Troponin T concentrations increase following AVR, and higher values are associated with prolonged aortic cross-clamp times, CPB times, and surgery duration.[29] Because these intraoperative events also lead to reduced myocardial function following cardiac surgery, we expected that reduced GLS would be associated with a postoperative increase in troponin concentration; however, we did not find an association. This investigation has limitations that are inherent to its retrospective design, including the possibility of unmeasured confounding variables. Further, our investigation could only assess association, not causation. While this investigation provides evidence that post-CPB GLS after AVR is associated with prolonged hospitalizations, this association was not tested in patients with aortic regurgitation or other types of cardiac surgery. Other intraoperative events unique to cardiac surgery, such as pericardiotomy, may also affect ventricular function; however, pericardiotomy has only a minimal impact on right ventricular function,[30] and a significant impact on left ventricular function is not expected. Furthermore, radial and circumferential strain were not included in this analysis and this investigation demonstrates associations with GLS only. Only four potential confounding variables were adjusted in our analysis due to sample size limitations. Therefore, results may be influenced by other patient and surgical characteristics that could not be included in the model.

In conclusion, our data suggest measurement of post-CPB GLS predicts postoperative outcomes better than pre-CPB GLS or Δ GLS%, and thus post-CPB GLS provides clinically relevant prognostic information in patients with aortic stenosis presenting for elective AVR. Post-CPB GLS also correlates with NT-proBNP. However, measurement of GLS was not associated with postoperative atrial fibrillation and Δ GLS% was not associated with any postoperative outcomes.

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Conflicts of interest

There are no conflicts of interest.

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