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A Comparison of Global Longitudinal, Circumferential, and Radial Strain to Predict Outcomes after Cardiac Surgery

Kan Zhang, M.D.¹ [Resident in Anesthesiology], Richard Sheu, M.D.² [Fellow in Cardiothoracic Anesthesia, Cleveland Clinic], Nicole M. Zimmerman, M.S.³ [Biostatistician], Andrej Alfirovic, M.D., F.A.S.E.⁴ [Associate Professor of Anesthesiology], Shiva Sale, M.D.⁵ [Staff Anesthesiologist], A. Marc Gillinov, M.D.⁶ [Judith Dion Pyle Chair in Heart Valve Research], and Andra E. Duncan, M.D., M.S., F.A.S.E.⁷ [Associate Professor of Anesthesiology]

¹Anesthesiology Institute, Cleveland Clinic Address: 9500 Euclid Avenue, Cleveland Clinic, Cleveland, OH 44195 zhangk@ccf.org

²Acting Assistant Professor of Anesthesiology, Department of Anesthesiology and Pain Medicine, University of Washington Medical Center, Seattle, WA Address: 9500 Euclid Avenue, Cleveland Clinic, Cleveland, OH 44195 sheurich@uw.edu

³Departments of Quantitative Health Sciences and Outcomes Research, Cleveland Clinic Address: 9500 Euclid Avenue, Cleveland Clinic, Cleveland, OH 44195 nicolezimm@gmail.com

⁴Department of Cardiothoracic Anesthesia, Cleveland Clinic Address: 9500 Euclid Avenue – J4, Cleveland Clinic, Cleveland, OH 44195 alfirea@ccf.org

⁵Department of Cardiothoracic Anesthesia, Cleveland Clinic Address: 9500 Euclid Avenue, Cleveland Clinic, Cleveland, OH 44195 sales@ccf.org

⁶Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic Address: 9500 Euclid Avenue, Cleveland Clinic, Cleveland, OH 44195 gillinom@ccf.org

⁷Department of Cardiothoracic Anesthesia and Outcomes Research, Cleveland Clinic Address: 9500 Euclid Avenue – J4, Cleveland Clinic, Cleveland, OH 44195 duncana@ccf.org

Abstract

Objective: Myocardial strain measured by speckle-tracking echocardiography detects subtle regional and global left ventricular dysfunction. Myocardial strain is measured in the longitudinal, circumferential, and radial dimension; however, it is unclear which dimension of strain is the best predictor of postoperative outcomes.

*Corresponding author: Andra E. Duncan, MD, MS, FASE, Departments of Cardiothoracic Anesthesia and Outcomes Research, Cleveland Clinic 9500 Euclid Avenue/J4, Cleveland, OH 44195. Phone: (216) 445-2372, duncana@ccf.org.

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Conflict of Interests: Dr. Andra Duncan, A. Marc Gillinov, Kan Zhang, Richard Sheu, Nicole M. Zimmerman, Andrej Alfirovic, and Shiva Sale, M.D. have no conflicts of interest to disclose.

Design: A secondary analysis of prospectively collected data from a clinical trial (NCT01187329)

Setting: The cardiothoracic surgical operating rooms of an academic tertiary-care center

Participants: Cardiothoracic surgery patients with aortic stenosis having aortic valve replacement with or without coronary artery bypass grafting enrolled in a clinical trial

Interventions: Myocardial deformation analysis from standardized investigative transesophageal echocardiographic examinations performed after induction of anesthesia.

Measurements and Main Results: We compared the ability of intraoperative global longitudinal (GLS), circumferential (GCS), and radial (GRS) strain to predict adverse postoperative outcomes, including prolonged hospitalization and the need for pharmacologic hemodynamic support, after cardiac surgery. The association of GLS, GCS, and GRS with prolonged hospitalization (>7 days) and the need for pharmacologic hemodynamic support with epinephrine or norepinephrine after cardiopulmonary bypass were assessed using separate multivariable logistic regression models with adjustment for multiple comparisons. Of 100 patients, 86 had acceptable measurements for GLS analysis, 73 for GCS, and 72 for GRS. Worse GLS was associated with prolonged hospitalization [odds ratio (98.3% CI) of 1.21 (1.01,1.46) per unit worsening in strain ($P=0.01$, significance criterion <0.0167)] and the need for inotropic support with epinephrine [odds ratio (99.2% CI) of 1.81 (1.10,2.97) per unit worsening in strain ($P=0.002$, significance criterion <0.0083)], but not norepinephrine. GCS and GRS were not associated with adverse outcomes.

Conclusion: Global longitudinal, but not circumferential or radial, strain predicts prolonged hospitalization and the requirement for inotropic support with epinephrine after aortic valve replacement.

Keywords

Cardiac surgery; Echocardiography; Myocardial function; Myocardial deformation imaging

Introduction

Myocardial global longitudinal strain measured by speckle-tracking echocardiography accurately evaluates left ventricular (LV) function, detects subtle regional and global LV dysfunction, and is a better prognostic indicator than LV ejection fraction (EF).^{1,2} Strain measures myocardial deformation in three dimensions: longitudinal strain measures myocardial shortening from base to apex; circumferential strain measures systolic shortening of the short axis of the ventricle; and radial strain measures myocardial thickening from endocardium to epicardium. Strain assesses the magnitude of ventricular contraction in these three dimensions, and identifying the dimension of strain with the greatest predictive ability could improve perioperative risk stratification. Longitudinal strain is the most commonly used, though whether intraoperative circumferential or radial strain measured by transesophageal echocardiography (TEE) better predicts postoperative outcomes than longitudinal strain has not been explored.

Diverse geometric changes in myocardial strain during disease progression may further affect the ability of strain to predict outcomes. Certainly, the longitudinal, circumferential, and radial dimension of strain are affected differently by disease.^{1,3} For example, the progression of aortic stenosis is characterized by divergence in the direction and magnitude of strain: longitudinal strain decreases, while circumferential strain increases in early stages of aortic stenosis.⁴ Interestingly, patients with aortic stenosis who develop a compensatory increase in circumferential strain and rotation are less symptomatic than those with reduced circumferential strain,⁴ suggesting circumferential strain may serve as the best predictor of adverse outcomes. Few reports, however, have examined the ability of circumferential or radial strain to predict postoperative outcomes. Identifying the most clinically important dimension of strain will improve assessment of myocardial function and the ability to predict postoperative morbidity and mortality.

We previously reported that intraoperative global longitudinal strain (GLS) measured by TEE identifies patients who require prolonged hospitalization after cardiac surgery.⁵ The aim of this investigation was to determine whether intraoperative global circumferential (GCS) or global radial strain (GRS) is a better predictor of postoperative outcomes than GLS. We hypothesized that GLS is a stronger predictor compared to GCS or GRS of prolonged hospitalization (>7 days) and the need for pharmacologic hemodynamic support in patients having aortic valve replacement (AVR) surgery.

Methods

Patient Population

With Institutional Review Board approval (IRB #10-526) and written consent from participating patients, we performed a secondary analysis of prospectively collected data from a randomized clinical trial entitled, “The effect of the hyperinsulinemic normoglycemia clamp on myocardial function and utilization of glucose”.⁶ The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT01187329). Briefly, the primary trial randomized patients to hyperinsulinemic normoglycemia (high-dose insulin with concomitant glucose infusion titrated to glucose concentration of 80-110 mg/dL) versus standard therapy (insulin treatment if glucose >150 mg/dL).⁶ Since myocardial strain was not different between randomized groups at baseline or after the intervention in the primary investigation, groups were combined for this investigation.

Patients, between 40 and 84 years of age, scheduled for AVR for aortic stenosis with or without coronary artery bypass grafting (CABG) ± minor procedure between January 2011 and August 2013 were screened for inclusion. Tricuspid valve repair, closure of patent foramen ovale, septal myectomy, left atrial appendage ligation, Maze or pulmonary vein isolation were considered minor procedures. Exclusion criteria included the presence of aortic insufficiency without aortic stenosis, contraindications for intraoperative TEE examination, suboptimal echocardiographic images that were unacceptable for speckle-tracking analysis (as determined by blinded investigator), and requirement for intraoperative hypothermic circulatory arrest.

Intraoperative Management

Standard ASA monitors were supplemented by arterial and central venous or pulmonary artery catheters. Midazolam was administered prior to induction for anxiety if needed. General anesthesia was induced with etomidate, fentanyl, and depolarizing or nondepolarizing muscle relaxants, and subsequently maintained with fentanyl and isoflurane. Surgery was performed with a full sternotomy or upper hemisternotomy. Routine strategies for initiation and separation from cardiopulmonary bypass (CPB) were followed. Intermittent antegrade and/or retrograde Buckberg's or del Nido cardioplegia solution buffered in cold blood was administered for cardioplegic arrest. Bioprosthetic valve replacement was performed in all surgeries. After CPB, epinephrine and/or milrinone were given to maintain thermodilution cardiac index 2.0 L/min/m^2 or to treat myocardial dysfunction assessed by TEE. Norepinephrine was given when cardiac index 2.0 L/min/m^2 and/or TEE assessment of myocardial function was considered adequate to maintain systemic vascular resistance $800 \text{ dyn}\cdot\text{sec/cm}^5$ and mean arterial pressure 90 mmHg following separation from CPB.

Conventional Echocardiographic Data Collection

A standardized TEE examination was performed following induction of anesthesia prior to surgical incision by one of three staff cardiac anesthesiologists who were certified in Perioperative Transesophageal Echocardiography from the National Board of Echocardiography. Intraoperative echocardiographic images were collected with Vivid S6 or Vivid E9 Ultrasound systems (GE Healthcare Vingmed Ultrasound AS, Horten, Norway) utilizing either a multi-plane phased array GE 6Tc-RS 2.9-8.0 MHz transducer or an active matrix 4D volume phased array 3.0-8.0 MHz transducer.

Conventional echocardiographic measures of systolic and diastolic function were collected from echocardiographic data as previously described.⁶ LVEF calculated by Simpson's bi-plane method using standard mid-esophageal four- and two-chamber views, trans-aortic valvular peak and mean gradients obtained from deep transgastric long axis views using continuous wave Doppler, aortic valve area calculated by the continuity equation, dimensionless index calculated using peak aortic and LV outflow tract velocity, and degree of aortic regurgitation were measured intraoperatively.

Echocardiographic Measurement of Myocardial Deformation

Echocardiographic data was digitally collected, stored, and analyzed offline by an experienced investigator (A.E.D.), using a software analysis program (EchoPAC v. 112, GE Healthcare Vingmed Ultrasound AS, Horten, Norway). Global strain was calculated by averaging the values measured at the segmental level in the same frame, consistent with American Society of Echocardiography (ASE) guidelines.⁷

Analysis for GLS included assessment of three echocardiographic images from the standard mid-esophageal 4-chamber, commissural, long-axis views (at 0, 60, and 120 degrees). Analysis of GCS and GRS strain were assessed from the mid-papillary LV short-axis view. Acquisition of LV short-axis basal and apical views were initially planned to complement the GCS and GRS measurements; however, few patients had sufficient visualization of both

basal and apical views which were adequate for tracking of myocardial segments. Thus to preserve sample size, GCS and GRS were analyzed from a single transgastric mid-papillary LV short-axis view (similar to other reports^{8, 9}). Frame rate was maintained between 40 and 90 Hz.

Two-dimensional strain analysis uses frame-by-frame tracking of a unique pattern of bright and dark pixels, or speckles, in grayscale (B-mode) sector images to assess myocardial deformation. The myocardium in each image is divided into six myocardial segments, which are individually assessed for “tracking” quality. If the software program deems a segment “unacceptable”, the user may override this designation if tracking quality appears adequate. Only images that contained at least 5 of 6 “acceptable” myocardial segments were included for GCS and GRS analysis. Because GLS is composed of 3 myocardial images, at least 15 of 18 segments were required for analysis. Additional detail describing the speckle-tracking analysis for myocardial deformation has been described previously.¹ We refer to the absolute value when describing a change in strain according to convention: for example, a change from -16 to -20% GLS is an increase (i.e. an improvement) in strain.^{1, 7}

Statistical Analysis

Due to limited sample size and to maintain consistency with previous analyses,⁵ we planned *a priori* to adjust in all analysis for 3 important potentially confounding variables:¹⁰ age, CPB duration, and concomitant CABG. All patients with acceptable echocardiographic images were included.

Primary analysis—Primarily, we assessed whether GLS, GCS, or GRS were associated with prolonged hospitalization (>7 days) among patients with aortic stenosis undergoing valve replacement using 3 separate multivariable logistic regression models adjusting for potential confounders. Each model only included one type of strain.

Secondary analysis—Secondarily, we assessed whether GLS, GCS, or GRS was associated with the need for post-CPB pharmacologic hemodynamic support with epinephrine or norepinephrine using 6 separate multivariable logistic regression models adjusting for potential confounders.

With an overall alpha of 0.05 for the primary and secondary analysis, we conservatively used a significance criterion of 0.0167 for each primary analysis (i.e., Bonferroni correction, 0.05/3) and 0.0083 for each secondary analysis (i.e., 0.05/6) to control for multiple comparisons. Analysis was completed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Graphs were created using R version 3.4.1 (The R Foundation, Vienna, Austria). Odds ratios for the association between GLS, GCS, and GRS are calculated using the absolute value of strain and reported as worsening (decreasing absolute value) of strain.

Sample size and power—One hundred patients enrolled in the primary randomized trial,⁶ but only 95 were eligible for this sub-investigation (Figure 1). Of the 95 remaining patients, 86 had acceptable GLS measurements, 72 had acceptable GCS measurements, and 73 had acceptable GRS measurements. To calculate power, we assumed a 30% incidence of prolonged hospitalization. We had 90% power at the 0.05 significance criterion to detect an

odds ratio as small as 1.27 per unit worsening in GLS, 1.15 per unit worsening in GCS, and 1.07 per unit worsening in GRS.

Results

Of 86 analyzed patients, 43 received hyperinsulinemic normoglycemic clamp treatment. Baseline, demographic, and surgical characteristics are summarized for the study population in Table 1 and Table 2. Data is presented as N (%), mean $\pm$ SD, or median [25th, 75th] as appropriate.

Primary analysis

Prolonged hospitalization was observed in 22 (26%) of patients with acceptable GLS measurements, 20 (28%) of those with acceptable GCS, and 21 (29%) with GRS. Worse GLS was significantly associated with prolonged hospitalization, with an estimated odds ratio (98.3% CI) of 1.21 (1.01, 1.46) per unit worsening of GLS ($P = 0.01$) (Table 3, Figure 2). However, neither GCS [odds ratios (98.3% CI) per unit worsening of 1.05 (0.94, 1.17); $P = 0.16$], nor GRS [1.055 (0.997, 1.117); $P = 0.02$, which was greater than the prespecified >0.0167 significance criterion] were associated with prolonged hospitalization.

Secondary analysis

Post-CPB epinephrine was used in 15 (17%) of the eligible GLS patients and 14 (19%) of the eligible GCS and GRS patients. Pre-CPB GLS was significantly associated with post-CPB epinephrine use, with an estimated odds ratio (99.2% CI) of 1.81 (1.10, 2.97) per unit worsening in GLS ($P = 0.002$) (Table 3, Figure 2). However, there was no association between GCS or GRS and post-CPB epinephrine use, with estimated odds ratios (99.2% CI) of 1.22 (0.91, 1.64) per unit worsening in GCS ($P = 0.07$), and 1.11 (0.99, 1.25) per unit worsening in GRS ($P = 0.02$). The probability of all outcomes predicted by GLS, GCS, and GRS is shown in Figure 3.

Post-CPB norepinephrine was used among 25 (29%) of patients with acceptable GLS measurements and 20 (27-28%) of patients with acceptable GCS and GRS measurements. There was no association between strain measured in any direction and norepinephrine use, with estimated odds ratios (99.2% CI) of 1.05 (0.87, 1.31) per unit worsening in GLS ($P = 0.49$), 1.00 (0.89, 1.13) in GCS ($P = 0.98$), and 0.99 (0.94, 1.05) in GRS ($P = 0.77$).

Discussion

Myocardial strain using speckle-tracking echocardiography better predicts adverse outcomes compared to LVEF in surgical and nonsurgical cardiac patients.^{1-5, 9, 11-16} We examined the ability of the longitudinal, circumferential, and radial dimensions of strain measured by intraoperative TEE to predict outcomes in patients having AVR. Our results demonstrate that only longitudinal strain, not circumferential or radial strain, was significantly associated with prolonged hospitalization and the need for inotropic support after CPB.

Our results are consistent with a several other investigations that examined the ability of GLS to predict outcomes using transthoracic echocardiography. For example, Saito et al.⁹

reported that GLS, but not GCS, predicted 30-day hospital readmission or death in patients with chronic heart failure. GLS, but not GCS or GRS, discriminated between those with adequate versus poor exercise tolerance in patients with aortic stenosis.³ GLS, but not GCS, was significantly associated with mortality, heart failure, or arrhythmias in patients with cardiac sarcoidosis.¹⁷ All of these investigations provide evidence that longitudinal myocardial function, not circumferential shortening or radial thickening, is associated with morbidity and mortality in these specific patient populations. Our current investigation is the first report to examine GCS and GRS measured during cardiac surgery with TEE in patients with concomitant anesthesia-induced alterations in loading conditions. Our report provides evidence that GLS measured intraoperatively by TEE is a clinically meaningful measurement compared with GCS or GRS in patients having AVR.

Longitudinal, circumferential, and radial strain change in divergent directions during the progression of myocardial disease,^{1, 3, 4, 9} which may contribute to the ability of strain to predict outcomes. Longitudinal strain decreases (worsens) while circumferential and radial strain are unchanged in asymptomatic patients with severe aortic stenosis;³ circumferential strain increases in hypertensive patients with LV hypertrophy while longitudinal and radial strain decreases;¹⁸ longitudinal strain decreases while circumferential strain increases in pediatric patients early after heart transplant.¹⁹

GLS was the strongest predictor of adverse postoperative outcomes in our investigation compared with GCS and GRS, possibly because it reflects the function of longitudinally-oriented subendocardial muscle fibers which are adversely affected in early stages of aortic stenosis.²⁰⁻²² Certainly, early dense development of subendocardial fibrosis²² likely contributes to abnormal longitudinal strain in patients with aortic stenosis. In contrast, circumferential strain, which largely reflects the circumferentially-oriented fibers in the mid-myocardial wall,²³ is preserved until later stages of disease. Because no myocardial fibers are arranged in a radial direction, radial strain reflects the thickening of the entire myocardial wall and does not indicate abnormalities at a specific myocardial segment, which may explain why radial strain did not detect early dysfunction compared with longitudinal strain. Besides, due to the drastic change of transmural myocardial fiber orientation,²³ GCS and GRS do not discriminate the contractibility of different LV wall layers, which may complicate the interpretation of short axis strain.^{2, 24} Interestingly, compared to transmural radial strain, evaluation of subepicardial and subendocardial components of radial strain may increase the accuracy of LV dysfunction and aortic stenosis severity assessment.²⁵

Strain evaluates regional and global myocardial deformation using an angle-independent echocardiographic measure of the change in myocardial length in the longitudinal, circumferential, or radial direction.^{1, 26} GLS is more widely used than circumferential or radial strain for several reasons. First, inter- and intra-observer variability are lower and thus reproducibility is higher with longitudinal strain.²⁷ Second, learning skills to master GLS analysis may be easier and faster, compared with GCS or GRS analysis.²⁸ Third, compared to EF, longitudinal strain consistently predicts adverse cardiac outcomes,^{2, 3, 11, 13-16} such as cardiac death, heart failure hospitalizations, malignant arrhythmias and the need of AVR in patients with aortic stenosis.^{11, 29, 30} Far fewer investigations examined the ability of GLS measured by intraoperative TEE to predict postoperative outcomes after cardiac surgery,^{5, 31}

and an investigation that compares the association between longitudinal, circumferential, and radial intraoperative strain measured by TEE with postoperative outcomes has not been previously reported.

Our investigation showed that GLS was strongly associated with the use of epinephrine. This result is not surprising since epinephrine is administered for myocardial dysfunction. In contrast, no dimension of myocardial strain was associated with a requirement for norepinephrine support following CPB, consistent with norepinephrine use for its vasoconstrictive effects, rather than inotropic support.

There are limitations to our analysis. Importantly, the results of this investigation depend upon the quality of echocardiographic imaging. Strain measurements are not fully standardized between vendors, software programs, and echocardiographic workstations.^{27, 32} Myocardial strain analysis is affected by load; however, our measurements were collected after induction of anesthesia and before surgical incision where hemodynamic changes were limited to the effects of anesthesia. Nevertheless, heart rate and other loading condition may have affected the measurements.¹ Fewer images were available for circumferential and radial strain analysis compared with the longitudinal strain analysis. However, inclusion of the LV mid-papillary short-axis view resulted in an acceptable number (about 80% of GLS) of images and allowed us to compare this approach to data from the longitudinal analysis, using an approach similar to other reports.^{8, 9}

The semi-automated strain analysis program on the echocardiographic workstation allows less user adjustment compared to the offline analysis. Our analysis, however, was performed offline using the full capabilities of this strain analysis software program. Measurement of circumferential and radial strain is not available on some automated programs on the workstation, though more may provide this option in the future, especially if evidence suggests that circumferential or radial strain is a clinically important indicator. This number of confounding variables included in the analysis was limited by the size of the study population.

In summary, our investigation demonstrated that global longitudinal, but not circumferential or radial, strain predicted prolonged hospitalization and requirement of epinephrine support after cardiopulmonary bypass in patients undergoing aortic valve replacement.

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Fig. 1.

Patient flow chart. LV=left ventricle; LVEF=left ventricular ejection fraction.

(a) Odds Ratio (98.3% CI) of Prolonged Hospitalization**Exposure** **(b) Odds Ratio (99.2% CI) of Epinephrine use****Exposure** **(c) Odds Ratio (99.2% CI) of Norepinephrine use****Exposure** **Fig. 2.**

Forest Plot of Odds Ratios. GLS = global longitudinal strain; GCS = global circumferential strain; GRS = global radial strain.

Fig. 3. Plots of the Estimated Probability for predicting prolonged hospitalization, epinephrine support and norepinephrine support for global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS).

Table 1.

Preoperative baseline patient characteristics, demographics, and medical history. Data is shown as N (%), mean $\pm$ SD, or median [IQR].

Variables	Study population (N = 86)
Demographics	
Age (year)	69 $\pm$ 10
Female gender, N (%)	27 (31)
BMI (kg/m ²)	31 $\pm$ 7
Medical history, N (%)	
Diabetes mellitus	23 (27)
Heart failure	13 (15)
Hypertension	20 (23)
Myocardial infarction	6 (7)
Pulmonary hypertension	14 (16)
Stroke	4 (5)
Peripheral vascular disease	8 (9)
Previous vascular surgery	3 (3)
Cardiogenic shock	0 (0)
Dialysis	0 (0)
2D LVEF	63 [56, 70]
Preoperative laboratory values	
Hematocrit (%) ^a	40 $\pm$ 5
Creatinine (mg/dL)	0.93 [0.82, 1.08]
NT-pro-BNP (pg/mL) ^b	287 [140, 627]
Aortic valve disease	
Peak transvalvular gradient (mmHg)	82 $\pm$ 21
Mean transvalvular gradient (mmHg)	49 $\pm$ 14
Dimensionless index	0.23 $\pm$ 0.05
Aortic valve area (cm ²) ^c	0.75 $\pm$ 0.18
Aortic insufficiency	
0	37 (43)
1 – 2+	43 (50)
3 – 4+	6 (7)

LV= Left ventricle; EF = Ejection fraction.

^aPreoperative hematocrit unavailable for 1 patient

^bPreoperative BNP unavailable for 13 patients

^cPreoperative aortic valve area unavailable for 8 patients

Table 2.

Surgical characteristics. Data is shown as N (%), mean $\pm$ SD, or median [IQR].

Surgical characteristics	Study population (N = 86)
Duration of surgery (min)	364 [306, 423]
Cardiopulmonary bypass (min)	86 [63, 118]
Aortic cross-clamp (min)	64 [49, 79]
Surgical procedure, N (%)	
AVR	46 (53)
AVR + CABG	22 (26)
AVR $\pm$ CABG + other ^a	18 (21)
Previous cardiac surgery, N (%)	21 (24)
Cardioplegia, N (%)	
Buckbergs	72 (84)
Del Nido	13 (15)
Microplegia	1 (1)
Myocardial strain	
GLS	-17.0 $\pm$ 3.6
GCS	-17.0 $\pm$ 6.4
GRS	30.9 $\pm$ 14.0

AVR = Aortic valve replacement; CABG = Coronary artery bypass grafting; GLS = global longitudinal strain; GCS = global circumferential strain; GRS = global radial strain.

^a Additional surgical procedures including minor procedures (7), aortoplasty (5), ascending aorta replacement (5), mitral valve repair (2) or replacement (1)

Table 3.

Primary and secondary analysis: associations between global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS) on prolonged hospitalization and post-cardiopulmonary bypass use of epinephrine and norepinephrine. Each row is a separate logistic regression model.

Primary analysis	N	Incidence (%)	Odds Ratio ^a (98.3% CI) ^b	P-value
Prolonged hospitalization				
GLS	86	22 (26)	1.21 (1.01, 1.46)	0.01 ^c
GCS	72	20 (28)	1.05 (0.94, 1.17)	0.16
GRS	73	21 (29)	1.055 (0.997, 1.117)	0.02
Secondary analysis			Odds Ratio ^a (99.2% CI) ^d	P-value
Post-CPB epinephrine use				
GLS	86	15 (17)	1.81 (1.10, 2.97)	0.002 ^e
GCS	72	14 (19)	1.22 (0.91, 1.64)	0.07
GRS	73	14 (19)	1.11 (0.99, 1.25)	0.02
Post-CPB norepinephrine use				
GLS	86	25 (29)	1.05 (0.87, 1.31)	0.49
GCS	72	20 (28)	1.00 (0.89, 1.13)	0.98
GRS	73	20 (27)	0.99 (0.94, 1.05)	0.77

CPB = cardiopulmonary bypass

^aOdds ratios estimated per unit worsening (decreasing absolute value) in strain based on separate multivariable logistic regression models adjusting for age, duration of surgery, and concomitant CABG.

^bPrimary analysis assessed at a 0.0167 significance criterion (i.e., 0.05/3, Bonferroni).

^cSignificant association between pre-CPB GLS and prolonged hospitalization ($P < 0.0167$).

^dSecondary analysis assessed at a significance criterion of 0.0083.

^eSignificant association between pre-CPB GLS and epinephrine use ($P < 0.0083$, Bonferroni).