Hyperinsulinemic Normoglycemia Does Not Meaningfully Improve Myocardial Performance during Cardiac Surgery

A Randomized Trial

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ABSTRACT

Background: Glucose–insulin–potassium (GIK) administration during cardiac surgery inconsistently improves myocardial function, perhaps because hyperglycemia negates the beneficial effects of GIK. The hyperinsulinemic normoglycemic clamp (HNC) technique may better enhance the myocardial benefits of GIK. The authors extended previous GIK investigations by (1) targeting normoglycemia while administering a GIK infusion (HNC); (2) using improved echocardiographic measures of myocardial deformation, specifically myocardial longitudinal strain and strain rate; and (3) assessing the activation of glucose metabolic pathways.

Methods: A total of 100 patients having aortic valve replacement for aortic stenosis were randomly assigned to HNC (high-dose insulin with concomitant glucose infusion titrated to normoglycemia) *versus* standard therapy (insulin treatment if glucose >150 mg/dl). The primary outcomes were left ventricular longitudinal strain and strain rate, assessed using speckle-tracking echocardiography. Right atrial tissue was analyzed for activation of glycolysis/pyruvate oxidation and alternative metabolic pathways.

Results: Time-weighted mean glucose concentrations were lower with HNC (127 ± 19 mg/dl) than standard care (177 ± 41 mg/dl; $P < 0.001$). Echocardiographic data were adequate in 72 patients for strain analysis and 67 patients for strain rate analysis. HNC did not improve myocardial strain, with an HNC minus standard therapy difference of −1.2% (97.5% CI, −2.9 to 0.5%; $P = 0.11$). Strain rate was significantly better, but by a clinically unimportant amount: −0.16 s^{-1} (−0.30 to −0.03 s^{-1}; $P = 0.007$). There was no evidence of increased glycolytic, pyruvate oxidation, or hexosamine biosynthetic pathway activation in right atrial samples (HNC, n = 20; standard therapy, 22).

Conclusion: Administration of glucose and insulin while targeting normoglycemia during aortic valve replacement did not meaningfully improve myocardial function. **(ANESTHESIOLOGY 2015; 123:272-87)**

MYOCARDIAL dysfunction is common in cardiac surgical patients and worsens postoperative outcomes. Despite improvement in myocardial protection strategies, certain patients remain at high risk for postoperative myocardial dysfunction and mortality, especially those with severe left ventricular (LV) hypertrophy.[1,2] Because hypertrophied hearts experience exaggerated contractile dysfunction from ischemia and reperfusion injury,[3,4] techniques to improve myocardial protection during cardiac surgery have been explored, including glucose–insulin–potassium (GIK) infusions.

Glucose–insulin–potassium is thought to provide cardioprotective benefits by increasing myocardial glucose uptake and improving coupling of glycolysis and glucose utilization.[5–7] These metabolic alterations improve myocardial

What We Already Know about This Topic

- Glucose–insulin–potassium infusions are thought to provide cardioprotective benefits by increasing myocardial glucose uptake and improving coupling of glycolysis and glucose utilization. The hyperinsulinemic normoglycemic clamp technique may enhance the myocardial benefits of glucose–insulin–potassium.
- This study investigated whether treatment with hyperinsulinemic normoglycemic clamp technique improves intraoperative left ventricular function in patients with aortic stenosis having aortic valve replacement surgery.

What This Article Tells Us That Is New

- Administration of glucose and insulin while targeting normoglycemia during aortic valve replacement did not meaningfully improve myocardial function.

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 249. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). The study results were presented at the American Society of Anesthesiologists annual meeting in New Orleans, Louisiana, on October 11, 2014.

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efficiency and recovery of postischemic cardiac function in the hypertrophied heart.[3] Insulin also provides important cardioprotective benefits that are independent of glucose concentrations.[8] For example, insulin administration during reperfusion reduces myocardial infarction *via* phosphatidylinositol 3-kinase/protein kinase B and p70s6 kinase–dependent signaling pathways.[8,9] Alternative metabolic pathways for glucose breakdown may also provide beneficial effects. Certainly, production of *O*-linked β-*N*-acetylglucosamine (O-GlcNAc) by the hexosamine biosynthesis pathway is associated with improved functional myocardial recovery.[9,10] Thus, provision of glucose and insulin has repeatedly demonstrated myocardial benefit in laboratory investigations.[7] Clinical reports examining GIK, however, are inconsistent. Some report that GIK administration during cardiac surgery improves hemodynamic measures[9,11] and diminishes myocardial enzyme release.[12,13] Others, though, have not found benefit.[14]

Why results diverge remains unclear: but one possibility is that hyperglycemia, which often accompanies GIK administration, and consequent adverse cellular effects[15,16] mitigate myocardial benefits. Interestingly, many investigations of GIK during cardiac surgery using stricter glucose control demonstrated beneficial effects, including improved cardiac output, decreased myocardial enzyme release, and metabolic benefits.[17–23] In contrast, results from investigations that tolerated hyperglycemia are inconsistent.[9,12,24] Thus, avoiding hyperglycemia during GIK infusion may enhance the myocardial benefits of GIK. The hyperinsulinemic normoglycemic clamp (HNC) technique, an insulin infusion administered with exogenous glucose, resembles GIK, except that normoglycemia is targeted. Thus, hyperinsulinemic normoglycemia may improve myocardial function, decrease cardiomyocyte injury, and, ultimately, improve outcomes after cardiac surgery

A second explanation for the divergent GIK results is that many previous investigations used hemodynamic indices as the primary determinant of GIK efficacy, including thermodilution cardiac output—a measure of myocardial contractility dependent upon heart rate and loading conditions. Indeed, results are strikingly inconsistent where some report improved cardiac output[9,12,22] and others have not.[13,21,25] In contrast, measures of myocardial deformation, specifically, longitudinal strain and strain rate, are both sensitive, accurate, and validated measures of myocardial performance.[26,27] Certainly, assessment of LV strain adds significant prognostic value and predicts mortality in patients with aortic stenosis and preserved LV ejection fraction.[28]

Our goal was to extend previous understanding by (1) determining whether targeting normoglycemia while administering a GIK infusion, specifically HNC, improves perioperative myocardial function in patients at high risk for ischemia–reperfusion injury; and (2) directly assessing benefits of HNC using an improved, sensitive, and validated echocardiographic measure of myocardial deformation, longitudinal strain, and strain rate. Specifically, we tested the primary hypothesis that treatment with HNC improves intraoperative LV function in patients with aortic stenosis having aortic valve replacement (AVR) surgery. Our secondary hypotheses were that intraoperative right ventricular (RV) function and postoperative LV function similarly improves with HNC treatment. We also tested whether HNC increases myocardial glucose uptake and utilization, activates alternative metabolic pathways, and decreases cellular markers indicative of ischemic injury.

Materials and Methods

Study Design and Subject Selection

This prospective, single-center, randomized, parallel-group, superiority trial was approved by the institutional review board at the Cleveland Clinic and registered on ClinicalTrials.gov (NCT01187329; http://clinicaltrials.gov/ct2/show/NCT01187329?term=hyperinsulinemic&rank=2). Written consent was obtained from each participant. Patients between 40 and 84 yr of age with severe aortic stenosis scheduled for AVR with or without coronary artery bypass grafting (CABG) between January 2011 and August 2013 at the Cleveland Clinic were screened for inclusion. Exclusion criteria included the presence of aortic insufficiency without aortic stenosis, contraindication for transesophageal echocardiography (TEE), poor-quality echocardiographic images that were unsatisfactory for speckle-tracking strain analysis (more than three unacceptable myocardial segments as deemed by a blinded investigator, A.E.D.), and requirement for intraoperative hypothermic circulatory arrest (see Supplemental Digital Content 1, http://links.lww.com/ALN/B152, which provides additional details regarding subject selection and study design.)

Randomization and Blinding

Patients were randomly assigned (1:1 with concealed allocation) to intraoperative glucose management with standard care or HNC. Randomization was implemented using a password-protected Web-based system that was accessed by research personnel upon entrance to the operating room. Randomization was computer generated using the PLAN procedure in SAS statistical software and stratified by the presence or absence of diabetes mellitus (any diabetes [type1/type2/diet-controlled] *vs.* no diabetes) and by need for CABG (yes *vs.* no) at time of AVR.

Intraoperative management of serum glucose concentrations, hemodynamic measurements, and echocardiographic assessment of aortic valve stenosis were not blinded. The primary outcome, intraoperative myocardial deformation measured by longitudinal strain and strain rate, and other two-dimensional and Doppler echocardiographic parameters were evaluated by a blinded investigator working off-line from coded echocardiographic recordings. Echocardiographic analysis of three-dimensional (3D) LV ejection fraction was performed by echocardiographic technicians

who were blinded to randomized group. All postoperative clinical and laboratory evaluations were similarly conducted by investigators blinded to group allocation.

Anesthesia and Surgery

Standard anesthesia monitors were supplemented by central venous or pulmonary artery catheters and TEE. Anesthetic induction involved administration of etomidate, fentanyl, midazolam, and a depolarizing or nondepolarizing muscle relaxant. Anesthesia was subsequently maintained with fentanyl, isoflurane, and nondepolarizing muscle relaxants. Surgery was performed through either a full midline sternotomy or a minimally invasive upper hemisternotomy. Routine strategies for heparinization and initiation and separation from cardiopulmonary bypass were followed. Cardiopulmonary bypass with intermittent antegrade and retrograde Buckberg or del Nido cardioplegia buffered in cold blood was used. In all cases, a bioprosthetic valve replacement was performed. Epinephrine was administered for low cardiac index (<2.0 $l \cdot min^{-1} \cdot m^{-2}$), and/or norepinephrine was given for low systemic vascular resistance (<700 $dyn \cdot s \cdot cm^{-5}$) after separation from cardiopulmonary bypass to maintain mean arterial pressures greater than 80 mmHg and cardiac index greater than 2.0 $l \cdot min^{-1} \cdot m^{-2}$.

Glucose Management

Patients randomized to standard therapy received intraoperative glucose management according to a conventional insulin protocol that involved initiation of insulin infusion when blood glucose was greater than 150 mg/dl during or after cardiopulmonary bypass. The insulin infusion was adjusted according to repeated blood glucose measurements, which were collected, analyzed, and reported from samples obtained for arterial blood gas analysis approximately every 30 to 90 min.

Patients randomized to glucose management with HNC received an insulin infusion of 5 mU kg^{-1} min^{-1} and a variable glucose (dextrose 20%) infusion supplemented with potassium (40 mEq/l) and phosphate (30 mmol/l). This insulin dose was selected for its ability to suppress free fatty acid production[21,29] and inhibit gluconeogenesis,[30] similar to other investigations examining the myocardial benefit of glucose and insulin infusion.[21,22] The insulin infusion was initiated after induction of anesthesia. Dextrose was infused at an initial rate of 40 to 60 ml/h when the serum glucose concentration decreased to less than 110 mg/dl and then titrated to target glucose levels of 80 to 110 mg/dl by measuring blood glucose concentrations approximately every 10 min with an Accu-Chek (Roche Diagnostics, Switzerland) glucose monitor. At sternal closure, the insulin infusion was decreased to 1 mU kg^{-1} min^{-1}, and the dextrose infusion was slowly weaned off during the next 2 to 4 h while maintaining blood glucose concentrations greater than 80 mg/dl.

Intraoperative time-weighted mean glucose concentration was calculated (equal to the sum of the product of the average of the two consecutive measurements and the time difference between the two measurements divided by the total glucose reading time).

Postoperatively, both groups received insulin treatment following the same postoperative intensive care unit (ICU) protocol. Blood glucose concentrations were measured from arterial blood gas analysis approximately every 2 h, and the insulin infusion was adjusted to maintain serum glucose less than 180 mg/dl on postoperative day 1.

Hypoglycemia was defined as blood glucose less than 40 mg/dl and treated by administration of 20% dextrose (25 to 100 ml).

Study Endpoints

Primary and Secondary Echocardiographic Endpoints. The primary outcome variables were intraoperative LV global longitudinal strain and strain rate measured at the end of surgery by TEE. Baseline values were obtained after induction of anesthesia.

Secondary study endpoints included (1) intraoperative RV systolic longitudinal strain and strain rate measured by TEE at the end of surgery; and (2) postoperative LV longitudinal strain, strain rate, and 3D LV ejection fraction measured by transthoracic echocardiography 3-to-5 days after surgery.

All echocardiographic data for calculation of myocardial global strain and strain rate were assessed off-line by an experienced investigator (A.E.D.), blinded to group allocation, using strain analysis software (EchoPAC; GE Healthcare Vingmed Ultrasound AS, Norway). Echocardiographic data for calculation of 3D LV ejection fraction were assessed by echocardiographic laboratory technicians blinded to group assignment.

Conventional Echocardiographic Data Collection. Transthoracic echocardiography was performed by echocardiographic technicians in the Cleveland Clinic Echocardiographic Laboratory within 30 days before surgery and repeated 3-to-5 days postoperatively. Intraoperative TEE study examinations were standardized and performed by one of the three experienced staff cardiothoracic anesthesiologists who are board certified in Perioperative TEE by the National Board of Echocardiography. Standardized TEE study examinations were performed after anesthetic induction before surgical incision and repeated near the end of surgery after sternal closure (see Supplemental Digital Content 2, http://links.lww.com/ALN/B153, Conventional Echocardiographic Data Collection, which provides additional details regarding transthoracic and TEE conventional echocardiographic methods.)

Echocardiographic Analysis of Myocardial Deformation Using Speckle-tracking Echocardiography. Myocardial strain and strain rate measured by speckle-tracking echocardiography provide robust measurements of myocardial deformation, which have been validated by sonomicrometry in animals and magnetic resonance imaging tagging in humans.[27] Echocardiographic data were digitally collected and stored for off-line analysis of myocardial deformation

with speckle-tracking analysis software (EchoPAC version 112). Because serial echocardiographic examinations were performed in each patient, images of the LV were collected at equally spaced intervals of 60° (*i.e.*, 0°, 60°, and 120°) of rotation of the transducer in efforts to reproduce identical images for each echocardiographic examination, while circumferentially describing global myocardial function. Thus, mid-esophageal four-chamber, commissural, and long-axis views were collected for speckle-tracking echocardiographic analysis of the left ventricle. A mid-esophageal four-chamber view centered on the right ventricle was collected for analysis of longitudinal strain and strain rate for the right ventricle. A frame rate between 40 and 90 Hz was used (see Supplemental Digital Content 2, http://links.lww.com/ALN/B153, Speckle-tracking Echocardiographic Analysis of Myocardial Strain and Strain Rate, which provides additional details regarding the software analysis of strain and strain rate using speckle-tracking echocardiography.)

For LV analysis, six-segment LV strain and strain rate measurements from three views, including the mid-esophageal four-chamber, two-chamber, and long-axis view, were averaged (total of 18 segments). All measurements that included at least 15 "acceptable" segments were included in the LV analysis. A sensitivity analysis examining the results when 16, 17, or 18 segments were considered "acceptable" was also performed. For RV analysis, strain and strain rate measurements from a single view, the mid-esophageal four-chamber view centered on the RV, were used. At least five of six "acceptable" myocardial segments (requiring three of three free wall segments) were required for analysis. LV and RV early diastolic strain rates were also assessed. All analyses of myocardial deformation were performed by the same investigator (A.E.D.). By convention, we refer to the absolute value when describing a change in strain or strain rate: for example, a change in strain from −16 to −20% is considered to be an increase or improvement (*i.e.*, more negative) in strain.

Hemodynamic and Other Clinical Data Collection. Clinical evaluation of hemodynamic data and myocardial performance included mean arterial blood pressure, central venous pressure, and pulmonary artery pressures and thermodilution cardiac output/cardiac index (in patients with pulmonary artery catheters). Requirement for pharmacologic and/or mechanical circulatory support was recorded. Postoperative events indicative of recovery status included time to freedom from mechanical ventilation, length of ICU stay, and duration of hospitalization. Hospital readmission and death within 30 days of surgery were recorded.

Laboratory Measures. *N*-terminal pro-brain natriuretic peptide was measured on arrival to the operating room and repeated at 24 h after surgery. Serum creatine kinase-MB isoenzyme was measured postoperatively at three 8-h intervals; the peak creatine kinase-MB concentration was compared between groups. Serum troponin-T was measured at 2:00 AM on the first postoperative day. The peak serum concentration of lactate during the first 24 postoperative hours, an indicator of tissue ischemia and predictor of worse outcomes in cardiac surgical patients,[31] was recorded.

Right Atrial Tissue Analysis. Right atrial tissue was collected in consecutive patients (who required right atrial cannulation for cardiopulmonary bypass) during venous cannulation and decannulation. Laboratory analysis assessed the effect of HNC on (1) glucose uptake and utilization, by assessment of key regulatory enzymes of the glycolytic (hexokinase I, hexokinase II, and glyceraldehyde 3-phosphate dehydrogenase) and pyruvate oxidation pathways (pyruvate dehydrogenase); (2) activity of alternative metabolic pathways, specifically the hexosamine biosynthesis pathway, characterized by levels of thrombospondin-1 and O-GlcNAc; (3) the cellular protective effects of HNC, by measurement of markers of cellular injury, which included proto-oncogenes c-*fos* and early growth response protein-1 (Egr-1). The first sample, acquired during venous cannulation before aortic cross-clamping, was collected between 1 and 3 h after initiation of the intervention and thus reflected enzymatic and cellular effects of the intervention (HNC *vs.* standard therapy). The second sample, obtained during venous decannulation, reflected the enzymatic and cellular effects of the intervention and ischemic injury from cardioplegic arrest (fig. 1).

The levels of markers in the sections of atrial tissues were assessed by immunohistochemistry (see detailed procedure description in Supplemental Digital Content 3, http://links.lww.com/ALN/B154, Supplemental Laboratory Methods, for laboratory methods of staining of the right atrial tissue cross-sections and image analyses). Representative images of all laboratory measurements are shown in Supplemental Digital Content 3, http://links.lww.com/ALN/B154, figs. 1 and 2.

Statistical Analysis

All prespecified analyses were conducted using an intention-to-treat approach and based on data available from 97 patients with aortic stenosis randomized to HNC or standard therapy.

Patients treated with HNC and standard therapy were compared on primary outcomes using analysis of covariance, adjusting for the corresponding baseline measurement (at beginning of surgery). A sensitivity analysis was performed to examine whether the results of the primary analyses of LV strain and strain rate were consistent if the analysis was limited to patients with 16, 17, or 18 "acceptable" myocardial segments.

Randomized groups were compared on secondary and exploratory outcomes which included (1) continuous outcomes using analysis of covariance or *t* test if no baseline measurements; continuous outcomes from the laboratory analysis of right atrial tissue used the repeated-measures analysis of covariance (main effect model unless $P_{\text{treatment} \times \text{time}} < 0.15$); (2) time-to-event outcomes using Cox proportional hazard regression; and (3) binary outcomes using chi-square tests. Intraoperative and postoperative laboratory continuous data were log-transformed in the model.

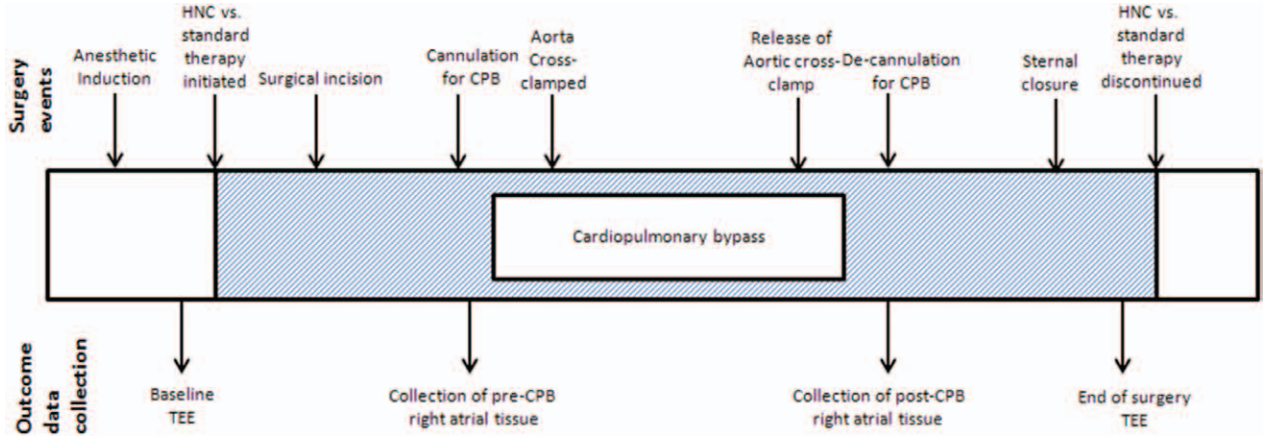

Fig. 1. Time line of study protocol depicting the study intervention (administration of hyperinsulinemic normoglycemic clamp [HNC] *versus* standard therapy; *shaded area*), surgical/anesthetic events, and collection of outcomes. CPB = cardiopulmonary bypass; TEE = transesophageal echocardiographic examination.

Intraobserver variability of the speckle-tracking analysis was assessed by repeating the analysis of one third of the baseline LV strain and strain rate examinations by the same investigator (A.E.D.) 3 or more months apart with no knowledge of the prior results. Statistical techniques included the Lin's Concordance Correlation that summarizes both the bias from the 45 degree line of equality and the correlation between two variables. Additional statistical methods included the Bland–Altman limits of agreement and the binomial exact method, which estimated the CI of proportion of difference (first–second reading) within acceptance limits.

Exploratory subgroup analyses were conducted to assess whether the effect of HNC on LV and RV systolic strain and strain rate was dependent upon patient age (≥75 *vs.* <75 yr), need for CABG, diabetes mellitus, and type of cardioplegia (Buckberg *vs.* other). An interaction between the HNC effect and a particular factor was considered significant if *P* value less than 0.15. We did not adjust for multiple comparisons across these variables.

Bonferroni correction was used to control type I error for testing two primary outcomes (*i.e.*, alpha = 0.05/2 = 0.025); corresponding 97.5% CIs were reported. The significance criterion for each secondary and exploratory outcome was *P* value less than 0.05 without adjusting for multiple testing. SAS software version 9.3 (SAS Institute, USA) was used for all analyses.

Sample Size Analysis

In a preliminary study (N = 5), we observed mean (SD) precardiopulmonary and postcardiopulmonary bypass global strain of −14% (5) and −11% (5), respectively, with mean (SD) of the difference of 3% (3). Assuming similar variability, 50 patients per group would detect a between-group difference of 1.7% (16% of observed postbypass mean) in mean within-patient change in global strain with 80% power at the 0.05 significance level.

With the attained total sample size of 72 for LV strain and observed SD of 4.6 for each group, we had 80% power at the overall 0.05 significance level (Bonferroni correction for two primary outcomes) to detect differences in mean strain of 3.4% or larger. Similarly, with an observed total sample size of 67 and SD of approximately 0.30, we had 80% power to detect differences of 0.23 s^{-1} or more in strain rate.

Results

Study Population

One hundred nineteen patients provided written consent. Eight patients did not fulfill inclusion/exclusion criteria, two patients were excluded because surgery was cancelled and nine were excluded because surgery was scheduled when none of the three study anesthesiologists were available to perform the study-specific echocardiographic examination. Thus, 100 patients remained, completing enrollment. Fifty patients (50%) were randomized to treatment with HNC and 50 to standard therapy. Three patients were excluded (in blinded manner during off-line echocardiographic review) because the echocardiographic images demonstrated valve pathophysiology that was predominantly aortic regurgitation rather than aortic stenosis (HNC, n = 1; standard care, n = 2). One additional patient in each group had a contraindication for TEE or inability to insert the TEE probe. Twenty-three patients were excluded from strain (HNC, n = 12; standard, 11) and 28 from strain rate (HNC, n = 15; standard, 13) analysis because of poor-quality echocardiographic images that were unsatisfactory for speckle-tracking analysis (more than three unacceptable myocardial segments). One patient was randomized to HNC but received standard care due to misinterpretation of the allocation assignment but was included in the HNC group under intention-to-treat rules (fig. 2).

Preoperative patient demographics, clinical characteristics, and preoperative echocardiographic measurements are

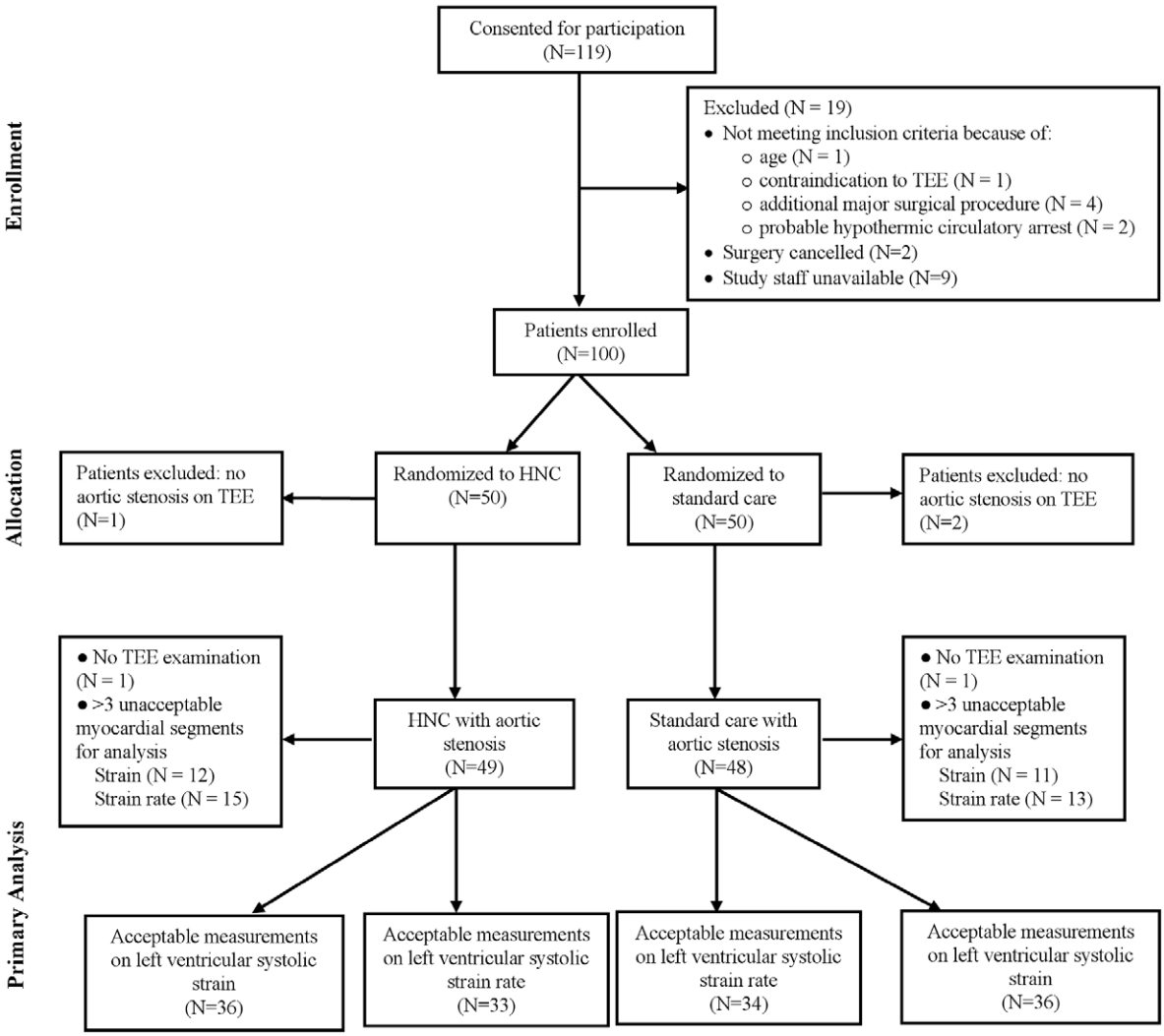

Fig. 2. Consolidated Standards of Reporting Trials flow diagram. HNC = hyperinsulinemic normoglycemic clamp; TEE = transesophageal echocardiographic examination.

shown in table 1. Patient groups were well balanced on most baseline variables except HNC patients had a larger body mass index. Intraoperative anesthesia and surgical variables as well as baseline echocardiographic and hemodynamic measurements are shown in table 2. Patients who received HNC had worse RV systolic strain and strain rate and lower LV ejection fraction. Other intraoperative variables were balanced between groups. Minor imbalances in patient characteristics may have occurred due to the relatively small study population.

Insulin infusion was administered to 48 patients (98%) in the HNC group at an average dose of 115 ± 50 units of insulin intraoperatively. Forty-three patients (90%) in the standard therapy group were treated with a conventional insulin infusion at an average intraoperative total dose of 22 ± 25 units of insulin. Intraoperative time-weighted mean glucose concentrations were lower in HNC patients (127 ± 19 mg/dl) than those receiving standard therapy (177 ± 41 mg/dl; $P < 0.001$). Hypoglycemia (glucose <40 mg/dl) did not occur.

Primary and Secondary Echocardiographic Outcomes

Intraoperative LV longitudinal global strain rate was improved (more negative) with HNC, but by a clinically unimportant amount (mean difference, −0.16; 97.5% CI, −0.30 to −0.03 s^{-1}; $P = 0.007$). HNC did not improve LV longitudinal strain or RV systolic strain or strain rate (all $P > 0.05$; table 3 and fig. 3). The HNC effect on LV strain did not depend on receiving epinephrine or norepinephrine (interaction $P > 0.15$). However, the effect on LV strain rate depended on norepinephrine use (interaction $P = 0.03$; mean difference was 0.06 s^{-1} [97.5% CI, −0.19 to 0.32 s^{-1}] with norepinephrine and −0.23 s^{-1} [−0.39 to −0.07 s^{-1}] without norepinephrine), but not on epinephrine (interaction $P = 0.71$).

The sensitivity analyses, which analyzed the results of the LV strain/strain rate analyses while including patients with 18, 17 or more, and 16 or more "acceptable" myocardial segments, demonstrated results consistent with the primary results reported above (see Supplemental Digital

Table 1. Demographics and Preoperative Echocardiographic and Laboratory Measures in HNC and Standard Therapy Groups in Patients with Aortic Stenosis (N = 97)

Variables	N	HNC (N = 49)	N	Standard (N = 48)	STD
Demographics					
Age (yr)	49	70 ± 9	48	70 ± 11	−0.01
Gender, female	49	13 (27)	48	17 (35)	−0.19
BMI (kg/m^2)	49	32 ± 9	48	29 ± 6	0.48
Medical history					
Diabetes mellitus	49	13 (27)	48	13 (27)	−0.01
Heart failure	49	8 (16)	48	7 (15)	0.05
Hypertension	49	12 (24)	48	12 (25)	−0.01
Myocardial infarction	49	4 (8)	48	4 (8)	−0.01
Stroke	49	3 (6)	48	2 (4)	0.09
Peripheral vascular disease	49	7 (14)	48	2 (4)	0.36
Cardiogenic shock	49	0 (0)	48	0 (0)	0
Dialysis	49	0 (0)	48	0 (0)	0
Preoperative echocardiographic measurements					
LV longitudinal systolic strain (%)	33	−17.3 ± 3.2	40	−16.8 ± 2.9	−0.16
LV longitudinal systolic strain rate (s^{-1})	33	−0.8 ± 0.2	39	−0.8 ± 0.2	0.03
Three-dimensional LV ejection fraction	29	58 ± 15	37	60 ± 8	−0.15
Aortic valve disease					
Peak transvalvular gradient (mmHg)	49	84 ± 23	47	81 ± 20	0.14
Mean transvalvular gradient (mmHg)	49	50 ± 15	47	49 ± 14	0.10
Dimensionless index	49	0.2 ± 0.0	48	0.2 ± 0.1	−0.29
Aortic insufficiency, N (%)	48		46		−0.02
0		21 (44)		19 (41)	
1–2+		23 (47)		26 (57)	
3–4+		4 (8)		1 (2)	
LV mass (g/m^2)					0.09
Female	12	112 ± 34	16	113 ± 39	−0.02
Male	35	144 ± 34	28	143 ± 40	0.02
End-diastolic thickness of the interventricular septum (cm)	47	1.4 ± 0.2	47	1.5 ± 0.3	−0.11
End-diastolic thickness of the posterior wall (cm)	47	1.2 ± 0.3	47	1.2 ± 0.2	0.03
LV end-diastolic dimension (cm)	47	4.6 ± 0.7	44	4.3 ± 0.7	0.41
Preoperative laboratory values					
Hematocrit (%)	48	41 ± 3	48	40 ± 5	0.26
Serum creatinine (mg/dl)	49	0.9 (0.8–1.1)	48	1.0 (0.8–1.1)	−0.06
NT-pro-BNP (pg/ml)	44	321 (179–717)	39	288 (128–948)	−0.01

Data are shown as N (%), mean ± SD, or median (interquartile range).

BMI = body mass index; HNC = hyperinsulinemic normoglycemic clamp; LV = left ventricle; NT-pro-BNP = *N*-terminal of prohormone brain natriuretic peptide; STD = standardized difference: the difference in means/proportions divided by the pooled SD, with an absolute STD ≥0.40 considered as imbalanced $\left(1.96 \times \sqrt{\frac{(n1+n2)}{n1 \times n2}} = 0.40\right)$.

Content 4, http://links.lww.com/ALN/B155, Echocardiographic Data Analyses and figure 1, which demonstrates the results of the sensitivity analysis and the distribution of the number of acceptable myocardial segments for the LV and RV analyses).

Exploratory subgroup analysis revealed a greater (more negative) effect of HNC on intraoperative LV strain and strain rate in patients who had CABG. HNC had a greater effect on strain rate in nondiabetic patients and those who received non-Buckberg cardioplegia (fig. 4).

Intraobserver Reliability. Intraobserver variability was good to excellent with the Lin's Concordance Correlation and Bland–Altman limits of agreement. The intraobserver agreements between the first and secondary readings were excellent with the Lin's Concordance Correlation (95% CI) of 0.94 (0.87 to 0.98) for strain and 0.93 (0.85 to 0.97) for strain rate, respectively. Bland–Altman statistical methods demonstrated good and consistent intraobserver reliability between the two readings. Bland–Altman plots of the difference between two readings *versus* the average of each pair of measurements show narrow widths of the 95% limits of agreement on strain and strain rate, with 95% CI of −2.4 to 1.7 on the difference in strain and −0.13 to 0.13 on the difference in strain rate, respectively. The proportions of differences were 100% within acceptance limits of ±20% for strain and strain rate (see Supplemental Digital Content 4,

Table 2. Baseline Intraoperative Echocardiographic and Hemodynamic Parameters and Perioperative Variables in HNC and Standard Therapy Groups in Patients with Aortic Stenosis (N = 97)

Variables	N	HNC (N = 49)	N	Standard (N = 48)	STD
Primary echocardiographic measurements					
LV systolic strain (%)	43	−17.0 ± 4.0	43	−17.1 ± 3.1	0.03
LV systolic strain rate (s^{-1})	42	−0.8 ± 0.2	42	−0.8 ± 0.2	0.16
Secondary intraoperative echocardiographic measurements					
RV systolic strain (%)	32	−21.0 ± 5.0	34	−23.1 ± 3.6	0.48
RV systolic strain rate (s^{-1})	32	−1.0 ± 0.2	36	−1.2 ± 0.3	0.59
Additional intraoperative echocardiographic measurements					
LV ejection fraction (%)	46	59 ± 15	45	64 ± 9	−0.45
Mitral lateral annular s' velocity (cm/s)	48	4 ± 2	45	5 ± 2	0.30
Mitral lateral annular e' velocity (cm/s)	48	5 ± 2	45	6 ± 2	−0.33
Mitral lateral annular a' velocity (cm/s)	47	5 ± 2	45	5 ± 2	0.10
Hemodynamic parameters					
Mean arterial pressure (mmHg)	49	86 ± 11	47	82 ± 11	0.35
Central venous pressure (mmHg)	48	16 ± 5	46	14 ± 6	0.31
Cardiac output (l/min)	31	4.3 ± 1.2	32	3.9 ± 0.7	0.36
Cardiac index (l min^{-1} m^{-2})	31	2.1 ± 0.5	32	2.0 ± 0.4	0.17
Intraoperative data					
Baseline glucose concentration (mg/dl)	49	123.5 ± 37.3	48	119.0 ± 31.4	0.13
Glucose concentration after release of aortic cross-clamp (mg/dl)	49	144.6 ± 43.2	47	201.7 ± 71.2	−0.97
Intraoperative time-weighted mean glucose concentration (mg/dl)	49	127 ± 19	48	177 ± 41	−1.57
Total insulin dose (units)	48	115 ± 50	43	22 ± 25	2.4
Hypoglycemia (≤40 mg/dl)	49	0 (0)	48	0 (0)	0
Fentanyl dose (mg)	48	1.0 ± 0.2	48	1.0 ± 0.2	−0.14
End-tidal isoflurane concentration (%)	35	1.3 ± 0.5	34	1.4 ± 0.5	−0.16
Surgical characteristics					
Duration of surgery (min)	49	359 (325–412)	48	373 (316–440)	−0.02
Duration of cardiopulmonary bypass (min)	49	89 (65–113)	48	86 (64–118)	0.03
Aortic cross-clamp (min)	49	69 (48, 77)	48	61 (49–83)	0.06
Surgical procedure, N (%)	49		48		0.16
AVR		26 (53)		24 (50)	
AVR + CABG		13 (27)		16 (33)	
AVR ± CABG + other procedures		10 (20)		8 (17)	
Tricuspid valve repair		0 (0)		1 (2)	
Maze procedure		1 (2)		1 (2)	
Aortoplasty		1 (2)		3 (6)	
Ascending aorta replacement		3 (6)		3 (6)	
Mitral valve replacement		1 (2)		0 (0)	
Mitral valve repair		2 (4)		0 (0)	
Septal myectomy		1 (2)		0 (0)	
Previous cardiac surgery, N (%)	49	13 (27)	48	10 (21)	0.13
Surgical incision, N (%)	48		48		0.18
Full stemotomy		34 (71)		30 (63)	
Mini stemotomy		15 (29)		18 (37)	
Cardioplegia, N (%)	49		47		0.28
Buckberg		43 (88)		39 (83)	
del Nido		5 (10)		8 (17)	
Microplegia		1 (2)		0 (0)	

Data are presented as mean ± SD, median (quartiles), or N (%).

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; HNC = hyperinsulinemic normoglycemic clamp; LV = left ventricle; RV = right ventricle; STD = standardized difference: difference in means/proportions divided by the pooled SD; absolute STD ≥ 0.40 considered as imbalanced.

http://links.lww.com/ALN/B155, Calculation of Intraobserver Variability Using Bland–Altman Limits of Agreement and Binomial Exact Method for additional details and figures demonstrating the results of the Bland–Altman analysis and details regarding the results of the binomial exact method).

Postoperative Echocardiographic Outcomes. Transthoracic echocardiography performed between postoperative days 3 and 5 showed similar 3D LV ejection fraction, strain, and strain rate in each group. Serum biomarkers indicative of myocardial function or injury were similar between groups (table 4).

Table 3. Primary, Secondary, and Exploratory Intraoperative Echocardiographic and Perioperative Clinical Endpoints in the HNC and Standard Therapy Groups in Patients with Aortic Stenosis (N = 97)

Variable	N	HNC (N = 49)	N	Standard (N = 48)	Difference (HNC Minus Standard) (97.5% CI)	*P* Value
Intraoperative echocardiographic parameters						
Primary outcomes						
LV systolic strain (%)*	36	−16.8 ± 4.6	36	−15.9 ± 4.6	−1.2 (−2.87 to 0.48)	0.11
LV systolic strain rate (s^{-1})*	33	−1.1 ± 0.3	34	−1.0 ± 0.3	−0.2 (−0.3 to −0.0)	0.007
Secondary outcomes					Difference (95% CI)	
RV systolic strain (%)*	26	−17.2 ± 4.3	28	−17.3 ± 3.7	−0.6 (−2.6 to 1.5)	0.57
RV systolic strain rate (s^{-1})*	26	−1.1 ± 0.3	28	−1.1 ± 0.4	−0.1 (−0.2 to 0.1)	0.45
Exploratory outcomes						
LV ejection fraction*	45	67 ± 14	43	66 ± 12	5 (0.1 to 9.0)	0.046
Systolic mitral annular velocity (s'; cm/s)*	47	7 ± 3	44	6 ± 2	2 (1 to 3)	0.001
Early diastolic mitral annular velocity (e'; cm/s)*	47	6 ± 2	44	5 ± 2	1 (0 to 2)	0.046
Late diastolic mitral annular velocity (a'; cm/s)*	46	6 ± 3	44	5 ± 2	1 (0 to 2)	0.23
Hemodynamic measures at the end of surgery						
Mean arterial pressure (mmHg)*	49	73 ± 9	47	76 ± 11	−3 (−7 to 2)	0.25
Central venous pressure (mmHg)*	48	15 ± 6	45	14 ± 6	1 (−3 to 2)	0.75
Cardiac output (l/min)*	36	5.4 ± 1.3	31	4.8 ± 1.4	0.3 (−0.3 to 0.9)	0.30
Cardiac index (l min^{-1} m^{-2})*	36	2.6 ± 0.5	31	2.4 ± 0.6	0.1 (−0.2 to 0.3)	0.5
Requiring epinephrine	49	9 (18)	48	9 (19)	0.98 (0.4 to 2.3)†	0.96
Requiring norepinephrine	49	19 (39)	48	11 (23)	1.7 (0.9 to 3.2)†	0.09
Requiring milrinone	49	2 (4)	48	2 (4)	0.98 (0.1 to 6.7)†	0.98
Hemodynamic measures 30 min after ICU admission						
Mean arterial pressure (mmHg)	45	80 ± 9	45	79 ± 10	1 (−3 to 5)	0.59
Cardiac output (l/min)	29	5.9 ± 1.4	32	5.3 ± 1.6	0.6 (−0.2 to 1.4)	0.13
Cardiac index (l min^{-1} m^{-2})	28	2.9 ± 0.6	32	2.8 ± 0.8	0.1 (−0.3 to 0.5)	0.60
Requiring epinephrine	49	8 (16)	48	7 (15)	1.1 (0.4 to 2.8)†	0.81
Requiring norepinephrine	49	14 (29)	48	5 (10)	2.7 (1.1 to 7.0)†	0.03
Requiring milrinone	49	1 (2)	48	0 (0)	NA	0.32
In-hospital time-to-event outcomes					Hazard Ratio	
Duration of mechanical ventilation (h)	49	5 (4, 6)	48	5 (3, 12)	1.2 (0.8 to 1.8)	0.38
Duration of ICU stay	49	27 (23, 51)	48	28 (22, 49)	1.0 (0.7 to 1.5)	0.97
Duration of hospital stay (days)	49	6 (5, 8)	48	6 (6, 8)	1.2 (0.8 to 1.8)	0.70
Postoperative binary outcomes					Relative Risk	
Hospital readmission within 30 days	49	1 (2)	48	1 (2)	0.98 (0.06 to 15)	0.99
30-day mortality	49	0 (0)	48	0 (0)	NA	NA

* The analysis adjusted for the corresponding baseline measurement. † Relative risk (95% CI).

HNC = hyperinsulinemic normoglycemic clamp; ICU = intensive care unit; LV = left ventricle; NA = not available due to zero event; RV = right ventricle.

Exploratory Outcomes

Intraoperative LV ejection fraction at the end of surgery was improved in patients assigned to HNC compared with standard therapy, but by a clinically unimportant amount (table 3). Intraoperative two-dimensional and Doppler echocardiographic measures of systolic and diastolic myocardial function were not different between groups, except for slightly higher mitral lateral annular systolic (s') and early diastolic (e') myocardial velocity in patients receiving HNC (for additional echocardiographic measures of diastolic function, see table in Supplemental Digital Content 5, http://links.lww.com/ALN/B156, Exploratory echocardiographic outcomes describing diastolic function).

Hemodynamic values at the end of surgery were similar in each group (table 3). Cardiac output and cardiac index were similar in patients assigned to HNC and those assigned to standard therapy. At the end of surgery and ICU admission, more HNC patients required vasopressor support with norepinephrine compared with patients receiving standard therapy. In-hospital outcomes (duration of mechanical ventilation, ICU, and hospital stay) were not different between groups.

Right Atrial Tissue Analysis

Key regulatory enzymes of the glycolytic (hexokinases I and II and glyceraldehyde 3-phosphate dehydrogenase) and pyruvate oxidation pathways (pyruvate dehydrogenase) were not different between groups (fig. 5). End-products of the hexosamine biosynthetic pathway (thrombospondin-1 and O-GlcNAc) and cellular markers of cardiomyocyte injury (c-*fos* and Egr-1) were not different between groups (fig. 6)

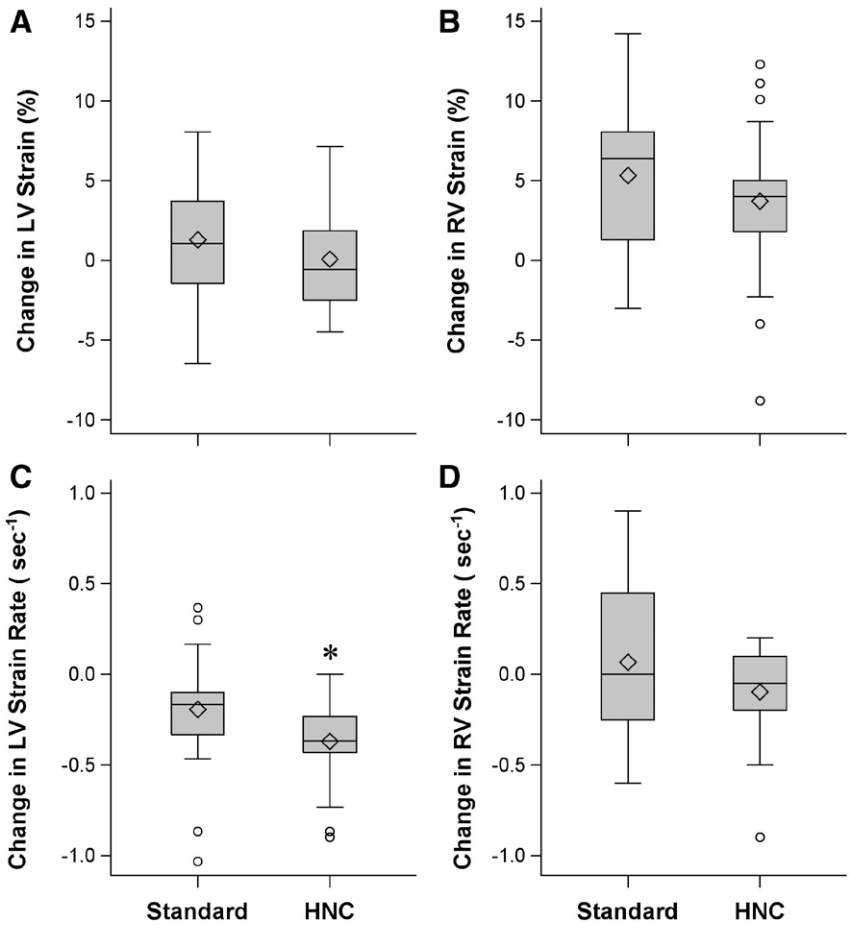

Fig. 3. Boxplots demonstrating changes in left ventricular (LV) and right ventricular (RV) strain (*A* and *B*) and strain rate (*C* and *D*) from beginning to end of surgery. Interquartile range (*boxes*), median (*horizontal lines*), high and low values within 1.5 interquartile range (*whiskers*), outliers (*circles*), and mean (*diamonds*) are shown. * *P* value is less than the significance level of 0.025 for two-group comparisons. HNC = hyperinsulinemic normoglycemic clamp.

(for detailed results of the laboratory analysis, see table, Supplemental Digital Content 3, http://links.lww.com/ALN/B154, Supplementary Laboratory Results for additional measures from right atrial tissue analysis).

Discussion

Our investigation improves upon previous reports of GIK by using a validated and reproducible measure of myocardial deformation, specifically, myocardial strain and strain rate. Myocardial strain, assessed by speckle-tracking echocardiography, measures longitudinal myocardial shortening,[32] which predicts outcomes in patients with acute myocardial infarction,[33] heart failure,[34] and after mitral valve surgery.[35] In contrast, other investigations used thermodilution cardiac indices as the primary measure of myocardial function,[18,22,36] an approach that is limited by the fact that cardiac output does not directly reflect contractile function—which may thus explain inconsistencies in previous reports. Myocardial strain and strain rate, however, are sensitive measures of the effect of HNC and are capable of detecting minor improvements in myocardial contractility.

Our initial analysis was designed to detect a change in strain of 1.7%. Although our final sample size was smaller than initially planned, the between-group difference in strain was less than our prespecified definition of a clinically meaningful change. This lack of effect on strain along with a minor, clinically unimportant change in strain rate suggests that HNC provides little, if any, improvement in myocardial function. Furthermore, the requirement for norepinephrine, which was higher in patients treated with HNC, overshadowed any effect of HNC on myocardial function. Furthermore, myocardial function assessed several days after surgery demonstrated no difference between groups. Our results thus provide no evidence that high-dose insulin and exogenous glucose meaningfully improves myocardial function in patients having AVR. We cannot rule out the possibility, however, that patients with more severe myocardial dysfunction may demonstrate a greater benefit.

Our results contrast with those from the Hypertrophy, Insulin, Glucose, and Electrolytes (HINGE) trial,[9] which was similarly performed in patients having AVR. The HINGE

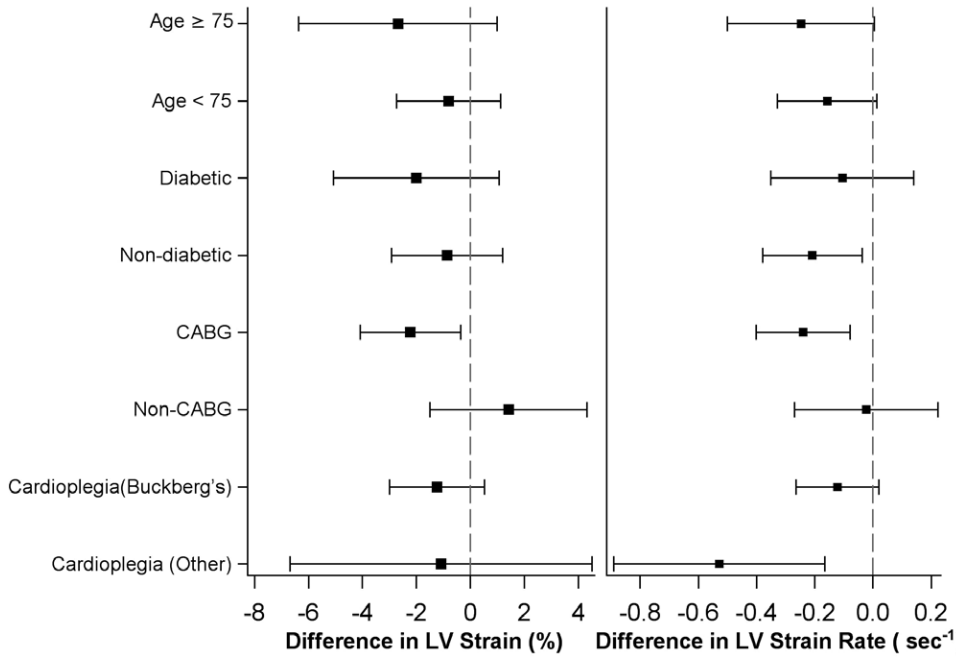

Fig. 4. Exploratory subgroup analysis of the difference (hyperinsulinemic normoglycemic clamp minus standard therapy) and 97.5% CI of left ventricular (LV) systolic longitudinal strain and strain rate. CABG = coronary artery bypass grafting.

Table 4. Postoperative Transthoracic Echocardiographic Parameters (Measured 3-to-5 Days Postoperatively) and Perioperative Laboratory Measures in HNC and Standard Therapy Groups in Patients with Aortic Stenosis

Variable	N	HNC (N = 49)	N	Standard (N = 48)	Difference (HNC Minus Standard) (95% CI)	*P* Values
Echocardiographic outcomes						
LV systolic strain (%)*	23	−14.3 ± 3.7	29	−15.2 ± 2.9	0.4 (−0.97 to 1.8)	0.54
LV systolic strain rate (s^{-1})*	21	−0.9 ± 0.2	28	−1.0 ± 0.2	0 (0.0 to 0.1)	0.27
Three-dimensional left ventricular ejection fraction (%)*	28	56 ± 10	31	58 ± 6	−1.4 (−5.1 to 2.4)	0.47
Laboratory outcomes					Ratio of Means (95% CI)	
NT-pro-BNP (pg/ml)*	42	1,465 (950 to 2,841)	39	1,868 (866 to 3,255)	0.9 (0.7 to 1.2)	0.50
Troponin-T (ng/ml)	47	0.45 (0.26 to 0.85)	47	0.42 (0.18 to 0.62)	1.3 (0.9 to 1.8)	0.23
Serum lactate (mmol/l)	49	2.1 (1.6 to 2.5)	48	2.4 (1.5 to 3.0)	1.0 (0.8 to 1.1)	0.60
Creatine kinase (U/l)	45	484 (374 to 786)	45	481 (368 to 897)	1.0 (0.7 to 1.4)	0.98
Creatine kinase-MB (ng/ml)	45	22 (16 to 33)	45	18 (13 to 29)	1.2 (0.9 to 1.6)	0.25

Data are presented as mean ± SD or median (interquartile range).

* The analysis adjusted for the corresponding baseline measurement.

HNC = hyperinsulinemic normoglycemic clamp; LV = left ventricle; NT-pro-BNP = *N*-terminal of prohormone brain natriuretic peptide.

trial demonstrated a lower incidence of a low cardiac output state in patients who received glucose and insulin.[9] However, the difference was not clinically important when cardiac output was compared as a continuous variable. Similar to our findings, postoperative troponin concentrations were not different between groups. The studies were not identical: for example, patients in the HINGE trial had more pronounced LV hypertrophy, and it is thus possible that they were at higher risk for ischemia–reperfusion injury. Approximately 50% of the patients in the HINGE trial had New York Heart Association class III or IV heart failure and required more perioperative inotropic and vasoconstrictor drugs, perhaps suggesting a sicker patient population. Our investigation did not collect data on heart failure classification; however, the severity of aortic valve stenosis and baseline LV ejection fraction was similar between investigations. Cardioplegia solution differed between investigations, which may have affected the results. Importantly, we aimed for normoglycemia, whereas hyperglycemia was tolerated in the HINGE trial.[9] Certainly, glucose concentrations after myocardial reperfusion were approximately 70 mg/dl lower in our investigation, whereas our insulin dose was significantly higher (5.0

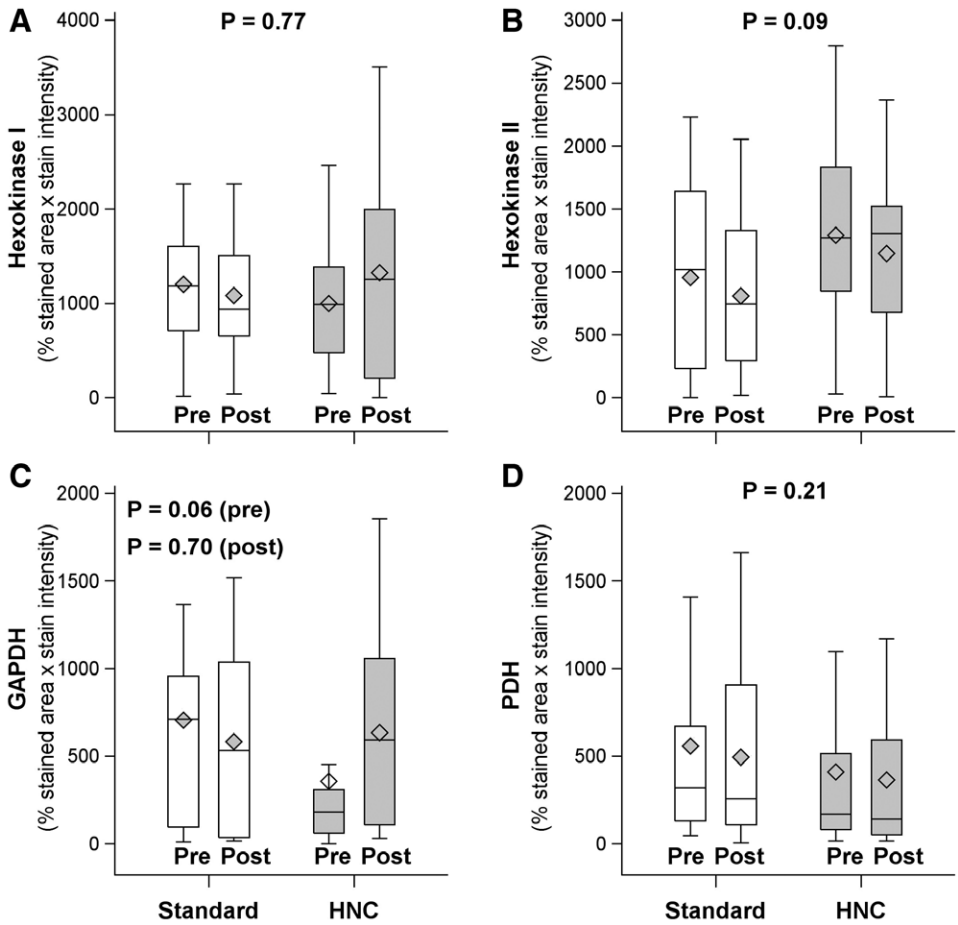

Fig. 5. (*A–D*) Boxplot demonstrating the distribution of laboratory measures before (pre-) and after (post-) aortic clamping on regulatory enzymes of the glycolytic/pyruvate oxidation pathway. If no interaction between time and treatment was found, we collapsed time and fit a main effect model. If interaction between time (pre- *vs.* post-) and treatment was significant ($P < 0.15$), we compared groups at each time. Extreme outliers are not shown. GAPDH = glyceraldehyde 3-phosphate dehydrogenase; HNC = hyperinsulinemic normoglycemic clamp group (*shaded boxes*); PDH = pyruvate dehydrogenase; Standard = standard therapy (*open boxes*).

vs. 0.875 $mU \cdot kg^{-1} \cdot min^{-1}$). Furthermore, we discontinued the insulin–glucose infusion upon completion of surgery, whereas the HINGE trial and others[9,12,13,36] continued GIK until 6 h after reperfusion. Other investigations, though,[37] reported no reduction in myocardial enzyme release with GIK infusions extending 12 or more hours postoperatively, suggesting that a longer duration of insulin administration may not have substantively altered our results. Finally, we compared within-patient changes in myocardial strain and strain rate, a sensitive study design because patients served as their own controls.

One explanation of our negative study results may be related to the fact that patients with aortic stenosis often have normal LV ejection fraction, thus providing little opportunity for improved LV function. This suggestion, however, conflicts with the results from the HINGE trial[9] as well as with evidence that the hypertrophied ventricle is highly susceptible to ischemic injury.[3,4] Despite a normal LV ejection fraction, LV strain is often abnormal in patients with aortic stenosis,[38] whereas RV strain worsened at the end of surgery. Thus, both RV and LV strain provide an opportunity for improvement with an effective myocardial protection technique. The negligible difference in these intraoperative measures of myocardial deformation between groups are consistent with a minimal benefit from intraoperative use of HNC, even though a significant number of echocardiographic image pairs (25 to 30%) in our investigation were not acceptable for myocardial deformation analysis. In addition, our clinical results were consistent with our laboratory findings. Certainly, the c-*fos* and *Egr*-1 genes, which are highly induced during acute ischemic episodes and thus serve as excellent measures of myocardial stress,[39] were similar between groups, providing no evidence of a cardioprotective benefit from HNC. It is worth considering that cardioplegic techniques have experienced considerable progress in recent years, and perhaps myocardial ischemia and reperfusion injury is adequately controlled during routine cardiac surgery and further enhancement with HNC may provide only minimal benefit.

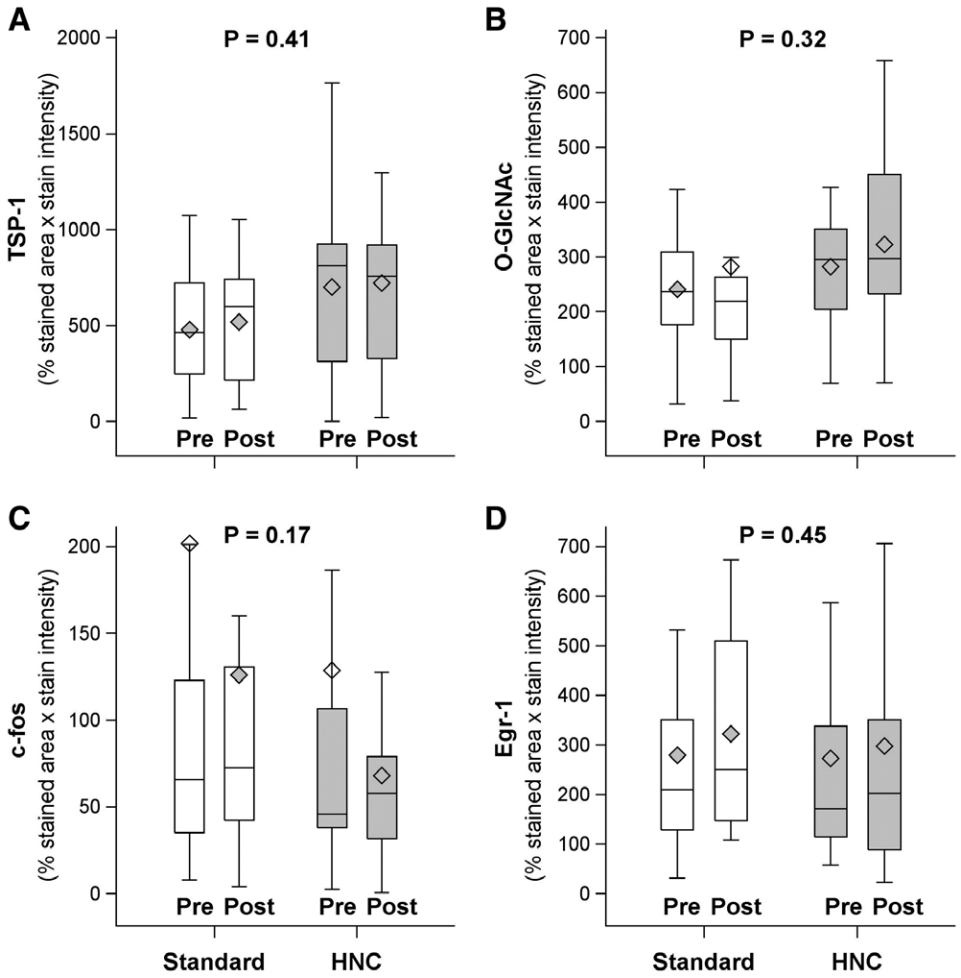

Fig. 6. (*A–D*) Boxplots demonstrating the distribution of laboratory measures before (pre-) and after (post-) aortic clamping examining adverse cellular and biochemical effects of hyperglycemia and cardioplegic arrest. Because there was no interaction with time, we collapsed time and fit a main effect model. Extreme outliers are not shown. Egr-1 = early growth response protein-1; HNC = hyperinsulinemic normoglycemic clamp group (*shaded boxes*); *O*-GlcNAc = *O*-linked *β*-*N*-acetylglucosamine; standard = standard therapy (*open boxes*); TSP-1 = thrombospondin-1.

The frequent use of insulin in the standard therapy group could also contribute to our negative results if similar myocardial protective benefits were provided to both groups. The glucose–insulin technique, however, was markedly different between groups. Our investigation did not measure insulin concentrations and thus cannot document that insulin concentrations were different between the two study groups. However, the amount of insulin administered was five-fold higher in the patients who received HNC. Certainly, other investigations have documented widely different serum concentrations with similar insulin doses,[40,41] so we believe that the difference in insulin concentrations between groups was considerable. Higher body mass index in the HNC group could suggest greater insulin resistance and possible blunting of the response to GIK; baseline fasting glucose, however, another reflection of insulin sensitivity, was similar between groups.

An increase in cardiac output with GIK as demonstrated in other reports may be explained by the hemodynamic effects of insulin. Insulin, a vasodilator that enhances skeletal muscle perfusion by capillary recruitment,[42] decreases afterload and thus increases cardiac output. Others similarly reported decreased systemic vascular resistance and/or higher requirement for vasoconstrictor with GIK, consistent with increased systemic vasodilation as a cause of increased cardiac output.[9,12,36] The requirement for inotropic support with epinephrine, however, a better reflection of the myocardial contractile state, was similar between groups.

Our investigation examined whether glycolysis and/or pyruvate oxidation was augmented as a result of HNC. The concentrations of enzymes characterizing the activity of the glycolytic pathway and pyruvate oxidation were similar between groups, suggesting that flux through these metabolic pathways was not increased. Because our patients had markedly increased LV mass, it is possible that hypertrophied hearts are less responsive to the effects of insulin on glucose oxidation than nonhypertrophied hearts, as has been demonstrated in laboratory studies.[43] We also examined whether

exogenous glucose may have entered alternative metabolic pathways, including the hexosamine biosynthesis pathway. End-products of the hexosamine biosynthetic pathway, however, were not different between groups. Our result contrast with others that reported a substantial increase in *O*-GlcNAcylation in patients given GIK,[9] possibly because of differences in glucose–insulin technique or our analysis of right atrial, rather than left ventricular tissue.

Although we targeted normoglycemia (80 to 110 mg/dl), our actual time-weighted mean glucose concentration was somewhat greater at 127 mg/dl, related largely to glucose-containing cardioplegia solution and efforts to avoid hypoglycemia. Nevertheless, average glucose concentrations in patients treated with the HNC were 50 mg/dl lower than patients receiving standard care and between 40 and 80 mg/dl lower than patients in other investigations.[9,12] It thus seems unlikely that the lack of benefit from HNC resulted from insufficiently tight glucose control. Indeed, the optimal glucose concentrations in cardiac surgical patients remains unknown, with some even reporting worse outcomes with normoglycemia than mild hyperglycemia.[44,45] Avoidance of hypoglycemia is important because of its association with mortality[46,47] and did not occur in our investigation.

Surgical procedure, surgical approach, and myocardial protection strategies varied somewhat among our study population, increasing the generalizability of these results. Our exploratory analysis, which examined the effect of HNC in various subgroups, were consistent in that they indicated a slight (although clinically unimportant) improvement in myocardial deformation parameters with HNC.

In summary, the use of intraoperative high-dose insulin with exogenous dextrose in high-risk cardiac surgical patients did not provide clinically meaningful improvements in myocardial contractility. There was no reduction in myocardial enzyme release or other hemodynamic benefit. Finally, key regulatory enzymes indicating an increase in myocardial glucose uptake and utilization were unchanged by HNC treatment as were cellular markers of ischemic injury. The effort, cost, and risk of hypoglycemia associated with HNC management do not seem justified.

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Competing Interests

Lifesciences (Irvine, California), Medtronic (Minneapolis, Minnesota), Tendyne (Roseville, Minnesota), Abbott (Abbott Park, Illinois), On-X (Toronto, Ontario, Canada), and PleuraFlow (Bend, Oregon). Dr. Gillinov has served as a speaker and/or received honoraria from Edwards Lifesciences, Medtronic, and Intuitive Surgical (Sunnyvale, California) and receives research support from St. Jude Medical (St. Paul, Minnesota).

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