Is Elevated Blood Glucose a Marker of Occult Tissue Hypoperfusion in Off-pump Coronary Artery Bypass Grafting?

Abstract

Context: Hyperglycemia has been found to occur during myocardial infarction and cardiac surgery even in nondiabetic patients. These being essentially stressful processes associated with hypoperfusion, we decided to find a possible relationship between the occurrence of global tissue hypoperfusion (GTH) and elevated blood glucose level in adult nondiabetic patients undergoing elective off-pump coronary artery bypass grafting (CABG). **Aims:** This study aims to observe for the occurrence of global tissue hypoperfusion and its effect on blood glucose level and whether raised blood glucose level can be used as a marker for GTH. **Design:** Prospective, observational study. **Settings:** Cardiothoracic operation theater and intensive care unit of a tertiary care teaching hospital. **Materials and Methods:** The occurrence of global tissue hypoperfusion were detected with the help of combined markers of mixed venous oxygen saturation and arterial lactate level at various perioperative study points together with arterial blood glucose level. Blood glucose level compared between the patients with and without GTH. **Statistical Analysis Used:** Numerical variables were compared between groups by Student's t-test and categorical variables by Fisher's exact test. Two-tailed $P \leq 0.05$ was considered for statistically significant. **Results:** The incidence of GTH was 67%. Blood glucose level was raised in patients with GTH at some study time points but with poor sensitivity and specificity values. **Conclusions:** Global tissue hypoperfusion is a common occurrence in even nondiabetic patients undergoing elective off-pump CABG. A relationship exists between rise in blood glucose level and global tissue hypoperfusion in such patients, although it cannot be viewed as marker of the same.

Keywords: *Hyperglycemia, hypoperfusion, nondiabetic, off-pump coronary artery bypass grafting*

Soumi Das,
Kakali Ghosh,
Avijit Hazra,
Chaitali Sen,
Anupam Goswami

Department of Cardiac Anaesthesiology, Institute of Postgraduate Medical Education and Research, Kolkata, West Bengal, India

Introduction

Perioperative hyperglycemia has been associated with increased perioperative morbidity and mortality, thereby increasing hospital cost and resource utilization, in diabetic and nondiabetic patients undergoing coronary artery bypass grafting (CABG).[1]

Severe hyperglycemia has been found to occur, even in nondiabetic patients, during stressful processes with limited cardiovascular reserve and inadequate perfusion, such as myocardial infarction and cardiac surgery.[1-8] In the early stages of shock, compensatory mechanisms are able to maintain blood flow to the important organs through peripheral vasoconstriction. Blood pressure, heart rate, arterial oxygen saturation, and urine output may be normal at this early stage although global tissue hypoperfusion (GTH) and lactic acidosis may occur.[9-11] Organ dysfunction could result from the imbalance between oxygen demand and supply due to prolonged tissue hypoperfusion[12-20] leading to increased cost and resource utilization.

Perioperative hyperglycemia being a common occurrence even in nondiabetic patients undergoing CABG; in our study, we hypothesized that this could be related to the occurrence of global tissue hypoperfusion. Combination of mixed venous oxygen saturation (SvO_2) and arterial lactate levels has been used to detect GTH. We also sought to determine whether elevated blood glucose level can be used as a marker to detect GTH and hence raise suspicion of underlying GTH, even when it is not hemodynamically apparent, so as to allow early intervention.

Materials and Methods

We conducted a prospective observational study in the cardiothoracic operation theater (OT) and Intensive Care Unit (ICU) of our tertiary care teaching

Address for correspondence:
Dr. Soumi Das,
14/B, D. L. Roy Street,
First Floor, Kolkata - 700 006,
West Bengal, India.
E-mail: soumidasanaesth79@gmail.com

How to cite this article: Das S, Ghosh K, Hazra A, Sen C, Goswami A. Is elevated blood glucose a marker of occult tissue hypoperfusion in off-pump coronary artery bypass grafting? Ann Card Anaesth 2018;21:393-401.

hospital between November 2015 and October 2016. Institutional Ethics Committee clearance was obtained beforehand. Being an observational study concerned with ascertaining the effectiveness of a possible diagnostic marker a formal sample size calculation was not done. We planned to recruit 100 consecutive adult nondiabetic patients undergoing elective off-pump CABG patients who fulfilled inclusion/exclusion criteria and provided written and informed consent. The selection criteria and working definitions we used have been listed in Table 1.

Our objectives were to detect the occurrence of GTH whether or not hemodynamically apparent (occult hypoperfusion) in our study patients, to examine the effect GTH on arterial blood glucose level, and to examine whether blood glucose level can be used as a

marker of occult tissue hypoperfusion in nondiabetic patients during and after elective off-pump CABG surgery. We also observed the total intraoperative blood loss in each patient,[23] duration of postoperative mechanical ventilation, moderate-to-high dose inotrope use, ICU stay, postoperative hospital stay, and multiple organ dysfunction score (MODS)[24] on days 1, 2, and 4 after surgery in each patient, together with occurrence of postoperative complications.

Data were collected from each patient at following predefined time points: preincision, i.e., immediately after induction of anesthesia and intubation, postprotamine, i.e., immediately after protamine administration, on arrival in ICU, 8 h after ICU arrival and 24 h after ICU arrival. Data captured included SvO_2, arterial lactate, arterial

Table 1: Subject selection criteria and working definitions used in the study

Category	Criteria and Definitions
Inclusion criteria[1]	Adult subject of either sex aged between 35-70 years
	Patients posted for elective off-pump CABG
	Ejection fraction ≥30% measured within 6 weeks before surgery
	Nondiabetic with HbA1C <6%
Exclusion criteria[1]	Left main stem coronary disease
	Associated heart valve pathology
	Intraoperative cardiac arrest
	Massive perioperative bleeding
	Presence of preoperative intra-aortic balloon pump
	Presence of cardiogenic shock or arrest
	Preoperative vasopressor therapy
	Preoperative mechanical ventilation
	Unfavorable laboratory parameters, i.e., creatinine >133 μmol/L (2.4 mg/dL), total bilirubin >22 μmol/L (0.39 mg/dL), white blood cell count >12,000/μL, or platelet count <100,000 cells/μL immediately before surgery
Working definitions	GTH: SvO_2 <70% and arterial lactate level ≥2 mmol/L[16]
	Moderate GTH: SvO2 <70% and lactate ≥2- <4 mmol/L[16]
	Severe GTH: SvO2 <70% and lactate ≥4 mmol/L[16]
	Occult hypoperfusion: Moderate-to-severe GTH with MAP ≥65 mmHg, CVP ≥8 mmHg, and UO ≥0.5 mL/kg/h[16]
	Overt tissue hypoperfusion: GTH with MAP <65 mmHg, CVP<8 mmHg and UO <0.5 mL/kg/h[16]
	Time of mechanical ventilation: Time from arrival in ICU postoperatively to extubation
	Duration of ICU stay: Number of hours after surgery to discharge from ICU. Patients were discharged from ICU when apyrexial, hemodynamically stable and requiring minimal use of vasoactive medication; chest drain output <1.5 mL/kg/h[16]
	Duration of hospital stay: Number of days after surgery to discharge from hospital[16]
	Massive perioperative bleeding: Bleeding requiring either transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period or reoperation after closure of sternotomy for the purpose of controlling bleeding (also known as BARC Type 4 [CABG-related] bleeding)[21]
	Moderate-to-high dose inotrope use: Moderate inotrope support was defined by inotrope use 12-24 h and high dose inotrope support was defined by support >24 h in this study
	Renal dysfunction or failure: Serum creatinine increase >177 μmol/L (3.19 mg/dL), serum creatinine increase >50%, or dialysis requirement[16]
	Prolonged ventilation: Ventilation after arrival in ICU for >24 h[22]

CABG: Coronary artery bypass grafting, HbA1c: Glycosylated hemoglobin, GTH: Global tissue hypoperfusion, SvO_2: Mixed venous oxygen saturation, MAP: Mean arterial pressure, CVP: Central venous pressure, UO: Urine output, ICU: Intensive Care Unit, BARC: Bleeding Academic Research Consortium

blood glucose, and vital parameters such as heart rate, invasive mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary artery pressure (mPAP), oxygen saturation (SO_2), and arterial blood gas (ABG) parameters as well as cumulative urine output (UO) in ml/kg/hour and perioperative bleeding. The data were collected by an anesthesiologist who was otherwise not involved in the intra- and post-operative management of the patient.

Anesthesia and monitoring were performed as per institutional protocol. Induction was done with intravenous opiate anesthetic (fentanyl 10–15 μg/kg) and intravenous thiopental (5–7 mg/kg). Intravenous rocuronium 1 mg/kg was used to achieve neuromuscular blockade. All patients were ventilated mechanically after intubation on 50% FiO_2 using oxygen, nitrous oxide mixture in 0.5 MAC isoflurane. Vascular access was achieved through a radial artery catheter for measurement of arterial blood pressure and blood sampling for arterial blood gas analyses, a multi-lumen internal jugular catheter for measurement of CVP and for fluid/medication administration, a pulmonary artery (PA) catheter to measure PA pressures and draw blood sample for measuring SvO_2. A Foley catheter with attached urometer was used to measure urine output and a nasopharyngeal temperature probe was employed to record body temperature. Two-lead electrocardiogram (leads II and V5) and BIS were also monitored continuously.

Postoperatively, the trachea was not extubated and shifted to ICU or recovery room using Bain's circuit and 100% oxygen for intermittent positive pressure ventilation. On arrival in the ICU, the patients were electively ventilated and managed by intensive care unit team following institutional protocol. Various parameters of the study as mentioned earlier were measured and recorded at the above-mentioned time points. Blood glucose value ≥180 mg/dL at any of the time points were corrected by intravenous bolus dose of human regular insulin in which case the glucose was rechecked ½ h later. Standard ICU protocol for postoperative care was followed. If cardiac index was <2.5 L/min/m² despite volume expansion to maintain a pulmonary capillary wedge pressure of 12–18 mmHg, dobutamine infusion was started. MAP was kept between 60 and 90 mmHg using dopamine or norepinephrine infusion.[5] Patients with massive perioperative bleeding were excluded from the study, and in others, blood hemoglobin (Hb) level was kept between 7 and 9 g/dL, with transfusion threshold at Hb <7 g/dL.[25] Patients were weaned from mechanical ventilation and subsequently extubated on fulfilling extubation criteria.[26]

Statistical analysis

Numerical variables were compared between groups by Student's independent samples *t*-test. Fisher's exact test was employed for intergroup comparison of categorical variables. Two-tailed $P ≤ 0.05$ was considered for statistically significant.

The approach of analysis adopted in this research included exploring the relationship between postoperative outcome variables with GTH and non-GTH patients. For this purpose, binomial logistic regression and ordinal logistic regression were carried out using the software SPSS Statistic 20, IBM, Washington D.C., United States. When the data of the outcome variables were either nominal or categorical such as those of "duration of ventilation" (nominal), renal failure, cardiac shock, and occurrence of death (categorical) the binomial logistic regression was carried out. In case of ordinal data like the MODS score, ordinal logistic regression was carried out. The results displayed the predicted probability of the "occurrence of the input variables" against for "occurrence of GTH" as the outcome variable. The regression analysis was done in two stages. In the first stage, all parameters were considered for the analysis. However, unrealistic values of Exp *(B)* of the odds ratio of the output tables required a multicollinearity test between the input variables. After removing variables that may possibly have multicollinearity, the regression was freshly carried out to establish the parameter estimates (predicted probability) of the input variables. Higher values of the parameter estimates (*B*) indicate stronger relationships with GTH patients over others. Similarly, a positive coefficient indicates a positive relationship-meaning that with unit increase in input variable, the probability of having GTH increases. On the contrary, a negative relationship indicates lower chances of having GTH. The goodness of fit of these relationships were further tested through the Hosmer and Lemeshow Test, Nagelkerke R^2 and Cox and Snell R^2 values. A 95% confidence interval (CI) values have been considered here and a two-tailed $P ≤ 0.05$ was significance test carried out. Further, the relationship between changes in SvO_2, lactate and glucose levels with the occurrence of GTH, was examined across five different time points including preincision stage, postprotamine stage, ICU baseline, ICU 8 h, and ICU 24 h stages. In this case, the predicted probability, however, was depicted against Non-GTH patients. Trend analysis was done, studying change in blood glucose levels with SvO_2 levels in GTH and non-GTH patients across all 100 data points. Linear trend lines were then mapped on the scattered plot diagrams. A possible correlation was also explored with changes in SvO_2, lactate and glucose levels, and outcome parameters across different time points. An R^2 value close to 1 is considered to be a strong correlation and vice versa. A statistical significance analysis was also carried out validate the correlations thus established. Receiver operating characteristic (ROC) curve analysis was done to ascertain if a cutoff can be identified with respect to maximum observed blood glucose value for predicting occult tissue hypoperfusion.

Results

Among 100 study participants, 67% (95% CI 57.78%–76.22%) encountered GTH at one or more

time points. Among the 67 who experienced GTH, based on hemodynamic criteria, 7 experienced overt tissue hypoperfusion at one or more time points, and the remaining 60 experienced only occult tissue hypoperfusion.

The flowchart in Figure 1 summarizes these figures.

Demographics

Mean age of patients with GTH (n = 67) was 57.7 ± 6.3 years and that of patients with no GTH (n = 33) was 54.4 ± 7.74 years; P = 0.024. Male:female ratio among patients with GTH was 59:8 and that in patients with no GTH was 27:6; P = 0.398. Mean fasting blood sugar of patients with GTH (n = 67) was 115.2 ± 16.62 mg/dl and that of patients with no GTH was 98.9 ± 14.86 mg/dl; P < 0.001.

Individual arterial blood glucose level at various time points

From Table 2, blood glucose levels were found to be higher for GTH patients compared to no GTH patients across preincision, ICU baseline, and ICU 8 h time points.
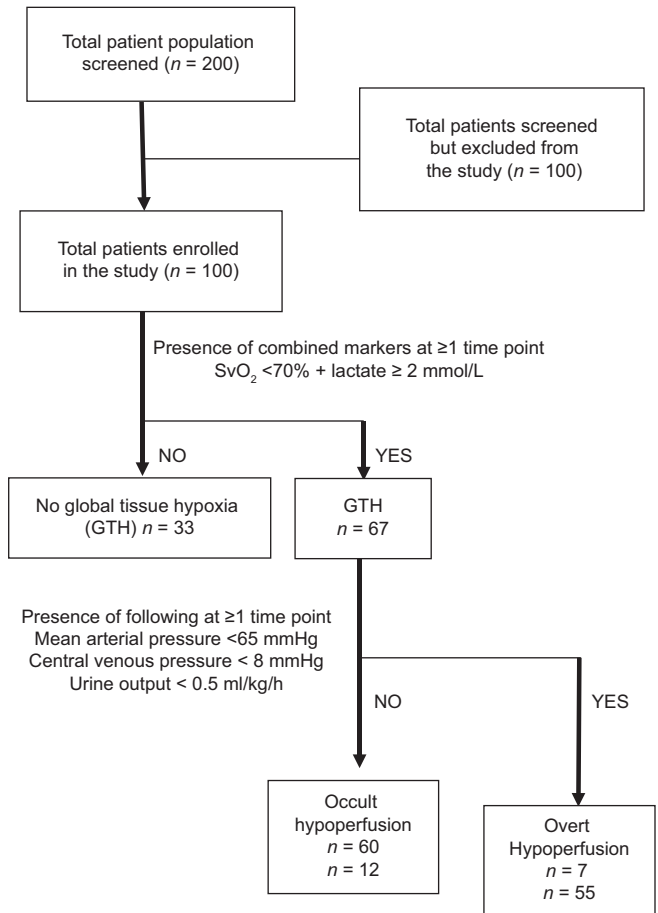
Trend analysis of blood glucose levels against mixed venous oxygen saturation and lactate levels, across different time points

Figure 2 shows the Trend Analysis of the performance of blood glucose levels in GTH patients against SvO$_2$ and lactate levels, across different time points. Results show that during postprotamine and ICU baseline time points, the blood glucose levels in GTH patients decrease with increase in SvO$_2$ levels. In case of lactate levels, results show a steep rise in blood glucose levels with increasing lactate levels during the preincision period, whereas the blood glucose levels moderately increase with increasing lactate levels across all time points.

Figure 3 shows the Trend Analysis of the performance of blood glucose levels in non-GTH patients against SvO$_2$ and Lactate levels, across different time points. Results show a steep upward trend in the blood glucose levels in Non-GTH patients with increase in SvO$_2$ levels, whereas the blood glucose levels are nearly stable with increase in SvO$_2$ levels across other time points. In case of lactate levels, results indicate stable blood glucose levels with increasing lactate levels in non-GTH patients, across all time points.

Arterial blood glucose level as a marker for occult tissue hypoperfusion

The proportion of patients who encountered occult tissue hypoperfusion in this study was 60% (95% CI
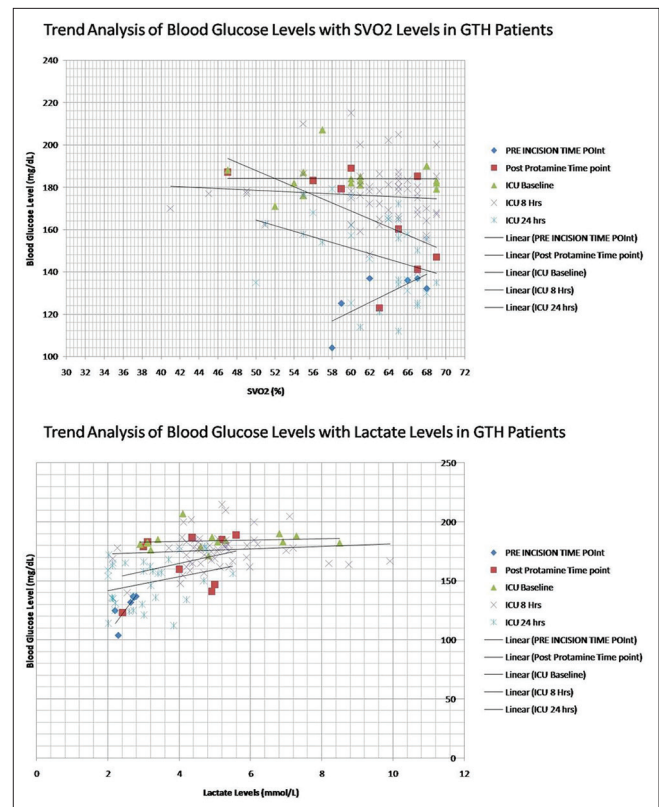

Figure 1: Global tissue hypoxia and tissue perfusion status of the study subjects. GTH: global tissue hypoxia/hypoperfusion, SvO$_2$: Mixed venous oxygen saturation

Figure 2: Trend analysis in GTH patients

Table 2: Changes in mixed venous oxygen saturation, lactate and glucose levels in no global tissue hypoxia or hypoperfusion versus global tissue hypoxia or hypoperfusion subgroups over time

	GTH patients			Non-GTH patients		
	SvO$_2$ (%)	Lactate	Blood glucose	SvO$_2$ (%)	Lactate	Blood glucose
Preincision						
Mean±SD	63.33±4.27	2.56±0.25	128.50±12.85	76.64±7.07	1.26±0.82	108.57±18.24
t	34.56	20.58	20.07	105.33	14.71	57.11
df	4	4	4	92	92	92
Significance (two-tailed)	0.000	0.000	0.000	0.000	0.000	0.000
Postprotamine						
Mean±SD	61.44±6.89	4.17±1.12	166.00±24.14	79.42±7.68	3.42±1.92	165.00±23.82
t	24.46	9.94	20.12	97.85	16.77	65.36
df	7	7	7	89	89	89
Significance (two-tailed)	0.000	0.000	0.000	0.000	0.000	0.000
ICU baseline						
Mean±SD	59.87±6.75	4.94±1.75	184.00±7.89	78.54±7.38	4.14±1.92	167.73±25.33
t	34.11	10.24	85.55	97.01	19.62	60.32
df	13	13	13	83	83	83
Significance (two-tailed)	0.000	0.000	0.000	0.000	0.000	0.000
ICU 8 h						
Mean±SD	62.53±5.53	5.22±1.39	177.37±12.95	74.81±6.00	4.55±1.96	170.23±22.49
t	71.96	26.00	92.94	82.24	15.43	48.47
df	46	46	46	41	41	41
Significance (two-tailed)	0.000	0.000	0.000	0.000	0.000	0.000
ICU 24 h						
Mean±SD	62.48±4.97	3.05±0.95	147.94±19.23	70.81±7.92	2.68±1.63	151.10±17.70
t	70.38	17.88	43.09	72.13	13.28	69.98
df	31	31	31	65	65	65
Significance (two-tailed)	0.000	0.000	0.000	0.000	0.000	0.000

GTH: Global tissue hypoxia or hypoperfusion, SvO$_2$: Mixed venous oxygen saturation, SD: Standard deviation, df: Degree of freedom, ICU: Intensive Care Unit

56.72%–75.28%). ROC curve analysis suggested that with a cutoff of ≤183 mg/dL, occult tissue hypoperfusion can be predicted with 54.6% sensitivity (95% CI 41.8%–66.9%) and 60.6% specificity (95% CI 42.1%–77.1%). However, the sensitivity and specificity figures are not high enough to make the cutoff clinically meaningful. The area under the ROC curve was 0.571 (95% CI 0.467–0.670) which also suggests that this cutoff can only be of limited clinical utility.

Relationship of GTH with postoperative outcome

From Table 3, GTH patients had higher MODS day 1 score, longer duration in ICU or hospital (highest correlation), increased operative blood loss.

From Table 4, the Odds Ratio for predictor variable duration of ventilation shows that GTH patients had increased duration of ventilation.

Correlation of individual mixed venous oxygen saturation, arterial lactate, and arterial blood glucose levels at various time points with postoperative outcome

Table 5 shows that SvO$_2$ at time point 24 h in ICU, has significant negative correlation with duration of inotrope use ($r = -0.431$, $P = 0.000$). Lactate level at preincision time point, have positive correlation with multi-organ

Table 3: Relationship between postoperative outcome variables (nominal and ordinal data) and global tissue hypoxia or hypoperfusion patients: Results using ordinal logistic regression

	B (parameter coefficient)	SE	Wald	df	Significance value	CI
GTH	11.447	5.185	4.874	1	0.027	95%
ICU stay	0.094	0.060	2.485	1	0.115	95%
Perioperative blood loss	0.004	0.002	3.444	1	0.063	95%
Hospital stay	3.164	0.808	15.349	1	0.000	95%
MODS score for day 1	−9.705	0.000		1		95%
MODS score for day 2	0[a]			0		95%

[a]This parameter is set to zero because it is redundant. df: Degrees of freedom, *B*: Parameter coefficient, Wald: Wald coefficient, SE: Standard error, CI: Confidence interval, GTH: Global tissue hypoxia or hypoperfusion, ICU: Intensive Care Unit, MODS: Multiple organ dysfunction score

dysfunction score on day 1 ($\rho = 0.171$, $P = 0.089$). Blood glucose level at postprotamine time point has significant positive correlation with duration of inotrope use ($r = 0.221$, $P = 0.027$).

Table 4: Relationship between postoperative outcome variables (nominal and categorical data) and global tissue hypoxia or hypoperfusion patients: Results using logistic regression)

	B	SE	Wald	df	Significance value	Exp (B)	CI
Duration of ventilation	0.215	0.114	3.550	1	0.060	1.240	95%
Moderate-to-high dose of inotrope	0.342	1.152	14.210	1	0.000	1.013	95%
cardiac shock	0.485	27,998.549	0.000	1	1.000	1.625	95%
Constant	0.210	27,998.550	0.000	1	1.000	1.233	95%

Predicted probability is for GTH (outcome variable). Exp(B) equivalent to Odds Ratio. df: Degrees of freedom, *B*: Parameter coefficient, Wald: Wald coefficient, OR: Odds ratio, SE: Standard error, CI: Confidence interval, GTH: Global tissue hypoxia or hypoperfusion
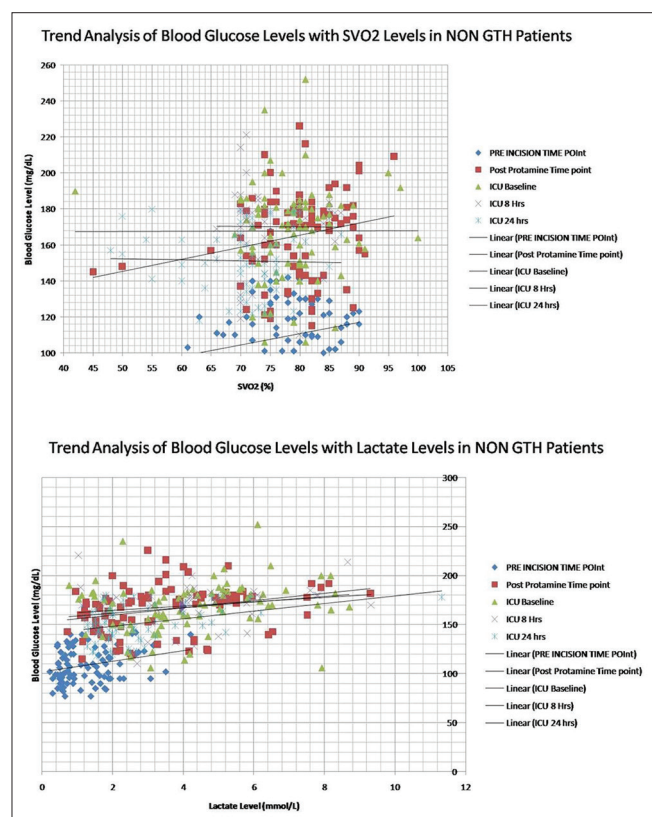

Figure 3: Trend analysis in non-GTH patients

Discussion

Overall tissue oxygen demand, if not met by adequate oxygen delivery by an optimal circulation, may lead to the state of global tissue hypoxia and act as a harbinger of multiorgan damage and failure when not managed appropriately at an early stage.[9,13-16] Mixed venous oxygen saturation and arterial lactate values may indicate GTH early, before conventional monitoring parameters, such as blood pressure and urine output, would indicate the same. Xu *et al.*[11] have documented significantly shorter hospital stay and lower ICU readmission rate in postcoronary bypass and valve surgery patients in whom hypoperfusion was detected at an occult stage ($ScvO_2$ <70%, lactate ≥2 mmol/L, and blood pressure ≥90 mmHg) and treated according to a standard protocol. In our study, combined markers of SvO_2 and arterial lactate level were used to detect global tissue hypoperfusion (GTH) as per

predefined criteria. GTH was detected in 67% of patients at one or more time points, with 55% having severe GTH at some point. The incidence of occult tissue hypoperfusion was 60%.

From previous studies, perioperative hyperglycemia appears to be common even in nondiabetic patients undergoing CABG both on-pump and off-pump. In a prospective observational study, Azarfarin *et al.*[27] found the prevalence of hyperglycemia (blood glucose ≥126 mg/dL) in 95% and severe hyperglycemia (blood glucose ≥180 mg/dL) in 54.6% of nondiabetic patients undergoing CABG. There was not much of a difference in the prevalence and intensity of hyperglycemia in patients undergoing CABG on-pump versus off-pump. One possible explanation for the rise in glucose could be inadequate circulation and consequent inadequate global perfusion and release of stress hormones. This being the hypothesis of our study comprising nondiabetic patients undergoing elective off-pump CABG, we identified subjects who encountered GTH and occult tissue hypoperfusion (those with GTH but apparently normal hemodynamics) and studied their arterial blood glucose level at various study time points. About 80% of our total study population reported high blood glucose level (>180 mg/dl) at some point or the other. About 25.3% of GTH patients reported high blood glucose level at postprotamine period, 40.2% of GTH patients at ICU baseline time point, 64.2% of GTH patients at ICU 8 h time point, and 0.01% of patients at ICU 24 h time point. Blood glucose levels were found to be higher for GTH patients compared to No GTH patients across preincision, ICU baseline and ICU 8 h time points. Therefore, raised blood glucose levels were found in most GTH patients post revascularization.

Trend Analysis of the performance of blood glucose levels in GTH patients against SvO_2 and Lactate levels, across different time points, show that during postprotamine and ICU baseline time points, the blood glucose levels in GTH patients decrease with increase in SvO_2 levels. In case of lactate levels, results show a steep rise in blood glucose levels with increasing lactate levels during preincision period, whereas the blood glucose levels moderately increase with increasing lactate levels across all time points. Therefore, in our study, increase in blood glucose level coincided with decrease in SvO_2 and increase in blood lactate level. The latter two being proven markers of

Table 5: Correlation of mixed venous oxygen saturation, lactate and glucose levels at various time points with postoperative outcome parameters

Variables	Preincision	Postprotamine	ICU at arrival	ICU at 8 h	ICU at 24 h
SvO2 (%)	75.84±7.61	77.80±9.18	75.74±9.88	67.67±8.62	68.06±8.08
Duration of ventilation (h)	−0.270 (0.006)	−0.324 (0.001)	−0.398 (0.000)	−0.320 (0.001)	−0.318 (0.001)
ICU stay (h)	−0.263 (0.008)	−0.343 (0.000)	−0.390 (0.000)	−0.367 (0.000)	−0.427 (0.000)
Hospital stay (days)	−0.177 (0.077)	−0.209 (0.037)	−0.363 (0.000)	−0.336 (0.001)	−0.367 (0.000)
MODS day 1	−0.056 (0.577)	−0.044 (0.665)	−0.090 (0.374)	−0.145 (0.150)	−0.275 (0.006)
MODS day 2	−0.209 (0.037)	−0.186 (0.064)	−0.196 (0.051)	−0.129 (0.201)	−0.166 (0.099)
MODS day 4	−0.162 (0.107)	−0.155 (0.123)	−0.138 (0.172)	−0.134 (0.183)	−0.117 (0.247)
Duration of inotrope use (h)	−0.192 (0.056)	−0.273 (0.006)	−0.428 (0.000)	−0.386 (0.000)	−0.431 (0.000)
Perioperative blood loss (mL)	−0.107 (0.289)	−0.096 (0.342)	−0.026 (0.796)	0.014 (0.894)	0.043 (0.669)
Lactate (mmol/L)	1.33±0.85	3.48±1.87	4.25±1.91	4.84±1.65	2.80±1.45
Duration of ventilation (h)	0.076 (0.455)	0.073 (0.468)	0.108 (0.283)	0.073 (0.473)	0.083 (0.411)
ICU stay (h)	0.050 (0.624)	0.006 (0.956)	0.030 (0.764)	−0.003 (0.975)	0.037 (0.717)
Hospital stay (days)	−0.055 (0.588)	0.046 (0.648)	0.038 (0.710)	0.075 (0.460)	0.023 (0.824)
MODS day 1	0.171 (0.089)	−0.072 (0.475)	0.021 (0.838)	0.063 (0.535)	0.052 (0.604)
MODS day 2	0.001 (0.990)	0.114 (0.259)	0.077 (0.448)	0.092 (0.365)	0.152 (0.131)
MODS day 4	0.145 (0.151)	0.134 (0.184)	0.141 (0.162)	0.145 (0.151)	0.115 (0.255)
Duration of inotrope use (h)	0.081 (0.423)	0.120 (0.234)	0.102 (0.311)	0.053 (0.602)	0.100 (0.322)
Perioperative blood loss (mL)	−0.058 (0.569)	−0.064 (0.525)	0.024 (0.813)	0.044 (0.663)	0.144 (0.153)
Glucose (mg/dL)	109.77±18.53	165.09±23.72	170.17±24.23	180.98±16.55	150.06±18.18
Duration of ventilation (h)	0.154 (0.127)	0.168 (0.094)	0.108 (0.286)	0.127 (0.209)	0.123 (0.225)
ICU stay (h)	0.118 (0.242)	0.159 (0.115)	0.077 (0.445)	0.111 (0.271)	0.048 (0.633)
Hospital stay (days)	−0.005 (0.957)	0.116 (0.251)	0.071 (0.480)	0.127 (0.210)	0.058 (0.564)
MODS day 1	0.093 (0.357)	0.083 (0.409)	0.092 (0.361)	0.194 (0.053)	−0.042 (0.677)
MODS day 2	0.125 (0.215)	0.183 (0.068)	0.132 (0.189)	0.099 (0.327)	0.121 (0.229)
MODS day 4	0.150 (0.137)	0.134 (0.184)	0.084 (0.408)	0.108 (0.285)	0.136 (0.178)
Duration of inotrope use (h)	0.102 (0.312)	0.221 (0.027)	0.106 (0.295)	0.139 (0.167)	0.086 (0.393)
Perioperative blood loss (mL)	−0.004 (0.967)	0.118 (0.242)	0.076 (0.454)	−0.088 (0.384)	0.083 (0.410)

Values of SvO$_2$, lactate and glucose levels are indicated as mean±SD. Other values indicate Pearson correlation coefficient *r* with the *P* value from hypothesis test of correlation in brackets for continuous variable including a) duration of ventilation, b) duration of stay in ICU, c) total duration of stay in hospital, d) duration of inotrope use, and e) perioperative blood loss. For ordinal data like MODS for day 1, day 2, and day 3, Spearman's correlation coefficient (ρ) has been used with the *P* value from hypothesis test of correlation in brackets. The *r* or ρ values have been interpreted as follows: ≥7.0 implies strong correlation; 0.5-0.7 implies good correlation; 0.3-0.5 implies moderate correlation and <0.3 implies poor correlation. Associated *P*<0.05 implies that the correlation observed in the sample is significant and that it is most likely to hold true for the underlying population. SD: Standard deviation, ICU: Intensive Care Unit, MODS: Multiple organ dysfunction score, SvO$_2$: Mixed venous oxygen saturation

GTH, the above findings go a long way in supporting our hypothesis that perioperative hyperglycemia is related to global tissue hypoperfusion.

Therefore, a possible explanation for the comparatively higher blood glucose level in the particular group of patients at certain time points could be due to global tissue hypoperfusion experienced by them at those points in time.

We took a step further to determine whether elevated blood glucose level can be used as a marker to detect GTH. However, the low sensitivity and specificity values we found implies that blood glucose level cannot be treated as marker of GTH and occult hypoperfusion in nondiabetic patients undergoing elective off pump-CABG, although it bears a relation to the occurrence of GTH. This could be because of factors other than global tissue hypoperfusion also contributing to the increase in blood glucose level.

Estrada *et al*.[1] have opined that the occurrence of perioperative hyperglycemia in nondiabetic patients undergoing CABG may be explained by stress hyperglycemia, glucose intolerance, or undiagnosed diabetes.

To summarize, postoperative outcome including complications in our study, patients with GTH spent longer duration in hospital and ICU, had higher operative blood loss and had higher MODS scores. Furthermore, patients with GTH had significantly long duration of ventilation, had high dose of inotrope use and were more likely to suffer a cardiac arrest.

Hu *et al*.[16] in their study, found that lactate at 24 h positively correlated with MODS on days 1, 2, and 7, ICU length of stay, and postoperative hospital stay. In our study, SvO$_2$ at time point, 24 h in ICU, had significant negative

correlation with duration of inotrope use, underlining the obvious fact that patients with inadequate circulation due to low cardiac output will require high dose of inotropes. Lactate level at preincision time point had a positive correlation with multi-organ dysfunction score on day 1. Blood glucose level at postprotamine time point had significant positive correlation with duration of inotrope use.

Conclusions

Global tissue hypoperfusion, identified using the combined markers of SvO_2 and lactate, was found to be a common occurrence in our study comprising nondiabetic patients undergoing elective off-pump CABG. The proportion of patients encountering occult tissue hypoperfusion was also high.

Our study finding also suggests that rise in blood glucose level in nondiabetic patients undergoing OPCABG may be an indicator of inadequate perfusion, raising the bar of suspicion for the same for the attending Cardiac Anaesthesiologist to initiate early intervention.

However, we are not able to propose elevated blood glucose level as a perioperative marker for GTH and occult tissue hypoperfusion. The confounding effect of other factors may be overshadowing the association between blood glucose and global tissue hypoperfusion. The exploration of blood glucose in conjunction with other factors will be the subject for further study.

Study limitations

Our study findings may need to be validated on a larger sample size before extrapolation and application in routine practice. In addition, in our study, due to logistic reasons, more than one cardiac surgeon, each with different surgical practice, performed the off-pump CABG surgeries, and this was not controlled for.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Estrada CA, Young JA, Nifong LW, Chitwood WR Jr. Outcomes and perioperative hyperglycemia in patients with or without diabetes mellitus undergoing coronary artery bypass grafting. Ann Thorac Surg 2003;75:1392-9.

2. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, *et al*. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.

3. Van den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, *et al*. Intensive insulin therapy in mixed medical/surgical intensive care units: Benefit versus harm. Diabetes 2006;55:3151-9.

4. Azarfarin R, Sheikhzadeh D, Mirinazhad M, Bilehjani E, Alizadehasl A. Do nondiabetic patients undergoing coronary artery bypass grafting surgery require intraoperative management of hyperglycemia? Acta Anaesthesiol Taiwan 2011;49:41-5.

5. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M. Attempting to maintain normoglycemia during cardiopulmonary bypass with insulin may initiate postoperative hypoglycemia. Anesth Analg 1999;89:1091-5.

6. Doenst T, Wijeysundera D, Karkouti K, Zechner C, Maganti M, Rao V, *et al*. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg 2005;130:1144.

7. Smith CE, Styn NR, Kalhan S, Pinchak AC, Gill IS, Kramer RP, *et al*. Intraoperative glucose control in diabetic and nondiabetic patients during cardiac surgery. J Cardiothorac Vasc Anesth 2005;19:201-8.

8. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, Williams BA, *et al*. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. Mayo Clin Proc 2005;80:862-6.

9. Shoemaker WC, Wo CC, Thangathurai D, Velmahos G, Belzberg H, Asensio JA, *et al*. Hemodynamic patterns of survivors and nonsurvivors during high risk elective surgical operations. World J Surg 1999;23:1264-70.

10. Rady MY, Rivers EP, Nowak RM. Resuscitation of the critically ill in the ED: Responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate. Am J Emerg Med 1996;14:218-25.

11. Xu R, Laine GA, Hu BY, Solis T, Bracey AW, Wilson JM, *et al*. Outcomes associated with a screening and treatment pathway for occult hypoperfusion following cardiac surgery. World J Cardiovasc Surg 2013;3:34-41.

12. Shoemaker WC, Appel PL, Kram HB. Role of oxygen debt in the development of organ failure sepsis, and death in high-risk surgical patients. Chest 1992;102:208-15.

13. Beal AL, Cerra FB. Multiple organ failure syndrome in the 1990s. Systemic inflammatory response and organ dysfunction. JAMA 1994;271:226-33.

14. Marshall JC. Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med 2001;29:S99-106.

15. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, *et al*. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.

16. Hu BY, Laine GA, Wang S, Solis RT. Combined central venous oxygen saturation and lactate as markers of occult hypoperfusion and outcome following cardiac surgery. J Cardiothorac Vasc Anesth 2012;26:52-7.

17. Pölönen P, Ruokonen E, Hippeläinen M, Pöyhönen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 2000;90:1052-9.

18. Ryan TA, Rady MY, Bashour CA, Leventhal M, Lytle B, Starr NJ, *et al*. Predictors of outcome in cardiac surgical patients with prolonged intensive care stay. Chest 1997;112:1035-42.

19. Christakis GT, Fremes SE, Naylor CD, Chen E, Rao V, Goldman BS, *et al*. Impact of preoperative risk and perioperative morbidity on ICU stay following coronary bypass surgery. Cardiovasc Surg 1996;4:29-35.

20. Ghotkar SV, Grayson AD, Fabri BM, Dihmis WC, Pullan DM. Preoperative calculation of risk for prolonged Intensive Care Unit stay following coronary artery bypass grafting. J Cardiothorac Surg 2006;1:14.

21. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, *et al*. Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the bleeding academic research consortium. Circulation 2011;123:2736-47.

22. Habib RH, Zacharias A, Engoren M. Determinants of prolonged mechanical ventilation after coronary artery bypass grafting. Ann Thorac Surg 1996;62:1164-71.

23. Sukprasert M, Choktanasiri W, Ayudhya NI, Promsonthi P, O-Prasertsawat P. Increase accuracy of visual estimation of blood loss

from education programme. J Med Assoc Thai 2006;89 Suppl 4:S54-9.

24. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ, *et al.* Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638-52.

25. Retter A, Wyncoll D, Pearse R, Carson D, McKechnie S, Stanworth S, *et al.* Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients. Br J Haematol 2013;160:445-64.

26. Higgins TL, Yared JP, Adi A. Postoperative respiratory care. In: Kaplan JA, Reich DL, Savino JS, editors. Kaplan's Cardiac Anesthesia: The Echo Era. 6th ed. Missouri, Unites States: Elsevier Saunders; 2011. p. 1046-60.

27. Azarfarin R, Alizadeh Asl A. Prevalence and intensity of hyperglycemia in non-diabetic patients undergoing coronary artery bypass graft surgery with and without cardiopulmonary bypass. Saudi Med J 2008;29:1294-8.