Diabetes Is Associated With Reduced Stress Hyperlactatemia in Cardiac Surgery

Giampaolo Greco,[1] Katherine A. Kirkwood,[1] Annetine C. Gelijns,[1] Alan J. Moskowitz,[1] and David W. Lam[2]

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OBJECTIVE

Hyperglycemia and hyperlactatemia are associated with increased morbidity and mortality in critical illness. We evaluated the relationship among hyperlactatemia, glycemic control, and diabetes mellitus (DM) after cardiac surgery.

RESEARCH DESIGN AND METHODS

This was a retrospective cohort study of 4,098 cardiac surgery patients treated between 2011 and 2015. Patients were stratified by DM and glucose-lowering medication history. Hyperglycemia (glucose >180 mg/dL), hypoglycemia (<70 mg/dL), and the hyperglycemic index were assessed postoperatively (48 h). The relationship between lactate and glucose levels was modeled using generalized linear regression. Mortality was analyzed using an extended Cox regression model.

RESULTS

Hyperglycemia occurred in 26.0% of patients without DM (NODM), 46.5% with DM without prior drug treatment (DMNT), 62.8% on oral medication (DMOM), and 73.8% on insulin therapy (DMIT) ($P < 0.0001$). Hypoglycemia occurred in 6.3%, 9.1%, 8.8%, and 10.8% of NODM, DMNT, DMOM, and DMIT, respectively ($P = 0.0012$). The lactate levels of all patients were temporarily increased with surgery. This increase was greater in patients who also had hyperglycemia or hypoglycemia and was markedly attenuated in patients with DM. Peak lactate was 5.8 mmol/L (95% CI 5.6, 6.0) in NODM with hyperglycemia vs. 3.3 (95% CI 3.2, 3.4) without hyperglycemia; in DMNT: 4.8 (95% CI 4.4, 5.2) vs. 3.4 (95% CI 3.1, 3.6); in DMOM: 3.8 (95% CI 3.5, 4.1) vs. 2.9 (95% CI 2.7, 3.1); and in DMIT: 3.3 (95% CI 3.0, 3.5) vs. 2.7 (95% CI 2.3, 3.0). Increasing lactate levels were associated with increasing mortality; increasing glucose reduced this effect in DM but not in NODM ($P = 0.0069$ for three-way interaction).

CONCLUSIONS

Stress hyperlactatemia is markedly attenuated in patients with DM. There is a three-way interaction among DM, stress hyperlactatemia, and stress hyperglycemia associated with mortality after cardiac surgery.

Hyperglycemia and hyperlactatemia are common manifestations of the metabolic response to a severe stress, such as cardiac surgery, and have been consistently associated with increased morbidity and mortality (1–3). Among these two phenomena, hyperglycemia has drawn the most attention from researchers, with glycemic control being the target of several studies and clinical trials (1,4). At present, however, strategies to improve glycemic control in a diverse patient population and whether stress hyperglycemia contributes to clinical outcomes or is merely a marker of illness severity remain unresolved and are highly controversial (5).

[1]International Center for Health Outcomes and Innovation Research (InCHOIR), Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY
[2]Division of Endocrinology, Diabetes and Bone Disease, Icahn School of Medicine at Mount Sinai, New York, NY

Corresponding author: Giampaolo Greco, giampaolo.greco@mountsinai.org.

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Glucose and lactate are interrelated components of the carbohydrate metabolism, each with the capacity to serve as a precursor for the biosynthesis of the other (6). Hyperlactatemia may arise from inadequate tissue oxygenation or other factors such as an accelerated rate of glycolysis (7). In cardiac surgery, hyperlactatemia has been consistently associated with hyperglycemia (8,9) and has been shown to be a better predictor of mortality than hyperglycemia when both are taken into account (10,11).

A number of observational studies have reported that the association between hyperglycemia and adverse outcomes is modified by preexisting diabetes mellitus (DM). In particular, the association between hyperglycemia and mortality is lacking or weaker among patients with DM compared with those without DM (NODM) (12–14). Moreover, in randomized clinical trials of "tight glycemic control," in which the intervention improved the outcomes of patients with NODM, no benefit was observed among patients with DM (15–17). Although the mechanism remains unclear, these findings suggest that DM confers a greater tolerance to stress-induced hyperglycemia and that a more permissive approach to glycemic control might be preferable with DM (18).

Given the interdependence between glucose and lactate in carbohydrate metabolism and the observation that DM weakens or abolishes the association between hyperglycemia and adverse outcomes, we hypothesized that DM might also influence the association of stress hyperlactatemia with adverse outcomes, including prolonged length of stay (LOS), hospital-acquired infections, pulmonary failure, and in-hospital mortality.

To our knowledge, no studies before this one have investigated the potential influence of DM on the relationship between stress hyperglycemia, stress hyperlactatemia, and outcomes after surgery. In this study, we tested our hypothesis using data from patients treated in the cardiothoracic surgery intensive care unit of a large U.S. academic medical center.

RESEARCH DESIGN AND METHODS

Patient Population and Clinical Settings

The study population consists of patients admitted between May 2011 and January 2015 to the Mount Sinai Hospital cardiothoracic surgery intensive care unit after undergoing cardiac surgery. Patients were selected using the ICD-9 procedure codes listed in the Supplementary Data and descriptions of the procedures from the institution's surgery database. From this initial selection we excluded *1*) patients undergoing transplantation or implantation of ventricular assist devices; *2*) patients with missing time of surgery; *3*) patients who underwent reoperations within 48 h; *4*) repeated hospitalizations from the same patient; and *5*) patients without postoperative glucose or lactate measurements. The selection of the study population is illustrated in Supplementary Fig. 1. The Icahn School of Medicine at Mount Sinai Institutional Review Board approved the investigation.

Outcomes and Definitions

Data were obtained from the Mount Sinai Hospital electronic data warehouse. Infections and respiratory failure were identified through ICD-9 codes (Supplementary Data), after exclusion of those reported as present on admission. Comorbidities were defined using ICD-9 codes from the enhanced Elixhauser definitions in combination with the "presence on admission" flag (19). Patients with DM, ICD-9 code (250.XX), were stratified by prior use of glucose-lowering agents. Groups included patients with NODM, with DM not treated (DMNT), taking oral medications (DMOM), or on insulin therapy alone or combined with oral medications (DMIT). Medication use before hospital admission was obtained as part of the "medication reconciliation" process or by a triage nurse for emergency department admissions. These data were queried using a comprehensive list of brand and generic names from all classes of glucose-lowering drugs, including insulins, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones, meglitinides, amylin analogs, incretin mimetics, sodium–glucose cotransporter 2 inhibitors, dipeptidyl peptidase 4 inhibitors, and biguanides. Glucose and lactate data included point of care and laboratory measurements. Glucose control during the first 48 h after the end of the surgical procedure was analyzed through continuous variables, such as the hyperglycemic index (HGI) (20), the time-weighted average, and the coefficient of variation (CV), and binary categorical variables such as hyperglycemia and hypoglycemia. The HGI was calculated as the area under the curve, defined by glucose levels $>$150 mg/dL (the threshold at which the Society of Critical Care Medicine recommends starting insulin therapy), divided by time (4).

Multiple measures were used to characterize glycemic control in this study as they complement each other's limitations (21). The time-weighted average reduces the potential bias due to unequal time intervals between measurements and is independent of a selected glucose threshold; however, this parameter alone could mask the possible presence of extreme values. HGI was used to represent the time spent with hyperglycemia, because it takes into account the duration and severity of hyperglycemia (21). Because low levels of lactate are not of significant clinical concern, as low glucose levels would be, we used time-weighted average and peak levels. Binary definitions of hyperglycemia and hypoglycemia are frequently used in the glycemic control literature for their simplicity and clinical face validity. For the binary definition of hyperglycemia and hypoglycemia, we used glucose thresholds of $>$180 mg/dL and $<$70 mg/dL, respectively (or $\leq$40 mg/dL for severe hypoglycemia) (4,22). In particular, hyperglycemia occurred if the area under the curve of glucose levels $>$180 mg/dL was $>$0, and hypoglycemia if the area above the curve of glucose levels $<$70 mg/dL (or 40 mg/dL) was $>$0. Hyperlactatemia was defined by a reading of blood lactate $\geq$4.0 mmol/L (23). Of the 120,132 lactate measurements analyzed in this study, 99.8% were performed by point-of-care testing with a reference range of 0.5–2.2 mmol/L using the GEM Premier 3000 Analyzer (Instrumentation Laboratory, Bedford, MA). For the remaining measurements (0.2%), the reference range of the assay performed was 0.5–1.6 mmol/L.

Statistical Analyses

Descriptive statistics were performed using the nonparametric χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Multiple pairwise comparisons between groups were performed using the Dwass, Steel, Critchlow-Fligner method. The Cochran-Mantel-Haenszel test for trend was used to test the statistical significance of the association between quartiles of HGI or time-weighted average lactate and outcomes. The relationship between

time-weighted average lactate and time-weighted average glucose, both assessed for the first 48 postoperative hours, was modeled using generalized linear regression. Mortality was modeled using a multivariable extended Cox regression model. Only the deaths that occurred 48 h after the end of the surgical procedure (after the glucose and lactate measurements) were included in the analysis. The same time frame (48 h after surgery = day 0) was used to calculate postoperative LOS. Pulmonary failure and infection were identified through ICD-9 codes that lack information on the time of diagnosis, except for whether it preceded admission or not. Covariates tested included demographics; insurance; procedure type and duration; type of admission (emergent, urgent, transfer, or elective); smoking status; number of days spent in the hospital before the surgery; Elixhauser comorbidities (19), with the exception of DM, which was used for group stratification; and glycemic parameters. Among the Elixhauser comorbidities, lymphoma, metastatic cancer, and nonmetastatic cancer were combined into one variable: cancer. Covariates for the final models were chosen via a backward selection procedure using the Schwartz information criterion. The analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

RESULTS

Characteristics of the Study Population

The study cohort included 4,098 patients. The baseline characteristics of the patients categorized by DM status are reported in Table 1. Patients with DM on average were older and included a higher percentage of minorities and a higher proportion of Medicaid and Medicare coverage than patients with NODM. Emergency admissions and transfers from other hospitals were also more common in patients with DM. Coronary artery bypass grafting (CABG) and valve operations together comprised more than 95% of all of the procedures performed. The frequency of these procedures varied between patients with DM and NODM. Whereas isolated CABG was the most frequent type of surgery performed in patients with DMOM and DMIT, valve surgery was the most common in patients with NODM and DMNT. Comorbidities that were differentially represented among the groups are reported in Table 1. With the exception of valvular disease, which was more prevalent among patients with NODM, other cardiovascular comorbidities, including hypertension, congestive heart failure, peripheral vascular disease, pulmonary circulation disorders, chronic pulmonary disease, and renal failure, were generally more prevalent in patients with DM, particularly in the groups with DMNT and DMIT. The prevalence of renal failure was four-times higher in patients with DMIT than in patients with NODM. Obesity also was more common among patients with DM, with a gradual increase of prevalence from DMNT to DMOM to DMIT.

Relationship Between Hyperlactatemia and Hyperglycemia

Glucose and lactate parameters, as assessed during the first 48 h after surgery, are reported in Table 2. Glucose measurements were more frequent in patients with DM than with NODM ($P < 0.0001$), albeit only slightly: the mean number of glucose measurements ranged from 26.4 in patients with NODM to 28.9 in patients with DMIT (NODM vs. DMIT: $P < 0.0001$). Time-weighted average glucose was lowest in NODM and highest in DMIT (NODM vs. any group: $P < 0.0001$), with intermediate levels in the groups with DMNT and DMOM (DMNT vs. DMOM: $P < 0.0001$; DMOM vs. DMIT: $P = 0.1187$). The CV and the proportion of patients with hyperglycemia (glucose >180 mg/dL) and hypoglycemia (glucose <70 mg/dL) during the first 48 h after surgery followed a similar pattern. Among all patients with hypoglycemia, nine (2.9%) presented severely low glucose levels (<40 mg/dL). Lactate measurements were slightly more frequent in the groups with DMNT and DMIT than those with NODM and DMOM ($P < 0.005$), with mean number of lactate measurements ranging from 19.1 to 21.0. The time-weighted average of lactate was lower in the patients with DMOM and DMIT than in those with NODM and DMNT ($P < 0.0001$). In contrast to hyperglycemia and hypoglycemia, hyperlactatemia was less frequent in DMIT patients (22.4%) than in NODM patients (36.6%) ($P < 0.0001$). When patients were grouped by surgery type, the same pattern was observed for patients who underwent CABG, valve surgery, or a combined CABG and valve procedure. Differences in hyperlactatemia were not significant for thoracic aortic aneurysm and other types of cardiac surgery, possibly due to the low number of subjects.

The glucose time-weighted average during the first 48 postoperative hours was associated with the lactate time-weighted average (Fig. 1*A*). However, although a steep increase occurred in lactate per unit increase of glucose in patients with NODM, only a modest increase was observed in patients with DM. In a similar manner, glycemic variability was associated with a marked increase in lactate in patients with NODM and a much more modest increase in patients with DM. The combined effect of glycemic variability and the time-weighted average glucose on lactate levels in patients with DM and with NODM is shown in Fig. 1*B*. When we used the traditional binary definitions for hyperglycemia (>180 mg/dL) and hypoglycemia (<70 mg/dL), patients who developed hyperglycemia or hypoglycemia had higher peak lactate levels than patients who did not (Fig. 1*C*). Moreover, peak lactate levels decreased progressively from NODM, having the highest peak, to DMNT, DMOM, and lastly DMIT with the lowest peak. The decrease in peak levels from NODM to DMIT was steeper among patients with hyperglycemia (or hypoglycemia) than among patients without (interaction between group and hyperglycemia: $P < 0.0001$; interaction between group and hypoglycemia: $P = 0.0104$). Seven of the nine patients with severe hypoglycemia had hyperlactatemia (>4 mmol/L).

To better characterize the changes in lactate levels during the perioperative period, patients with DM and with NODM were divided in two groups by whether their time-weighted average glucose during surgery was above the median, "high," or below the median, "low." All patients had a marked increase in lactate levels starting with surgery, which subsided ~18–24 h after the end of surgery (Fig. 1*D*). Patients in the "high" group had higher intraoperative and postoperative levels of lactate than those in the "low" group. DM was associated with a marked reduction of the surgery-induced increase of lactate levels in the "high" (glucose above the median) group.

Lactate, Glucose, and Outcomes

To assess the relationship of glucose, lactate, and adverse outcomes, we first divided the patient population in quartiles of HGI and quartiles of time-weighted

Table 1—Characteristics of study subjects

	NODM *n* = 2,584	DMNT *n* = 527	DMOM *n* = 559	DMIT *n* = 424	*P* value
Age (years)	61.8, 63.0 (53–73)	65.3, 66.0 (57–74)	64.9, 65.0 (58–72)	65.9, 66.0 (58–74)	<0.0001
Male sex	1,594 (61.7)	335 (63.6)	373 (66.7)	248 (58.5)	0.0449
Race/ethnicity					
White	1,713 (66.3)	218 (41.4)	181 (32.4)	137 (32.3)	
Black	197 (7.6)	79 (15.0)	57 (10.2)	64 (15.1)	
Hispanic	57 (2.2)	22 (4.2)	16 (2.9)	17 (4.0)	
Asian	110 (4.3)	48 (9.1)	42 (7.5)	30 (7.1)	
Not provided	507 (19.6)	160 (30.4)	263 (47.0)	176 (41.5)	
Insurance					<0.0001
Commercial	1,133 (43.8)	139 (26.4)	147 (26.3)	83 (19.6)	
Medicaid	317 (12.3)	108 (20.5)	138 (24.7)	104 (24.5)	
Medicare	1,099 (42.5)	276 (52.4)	270 (48.3)	235 (55.4)	
Other	35 (1.3)	4 (0.8)	4 (0.7)	2 (0.5)	
Admissions					<0.0001
Elective	1,694 (65.6)	271 (51.4)	337 (60.3)	204 (48.1)	
Urgent	215 (8.3)	39 (7.4)	22 (3.9)	19 (4.5)	
Emergent	183 (7.1)	77 (14.6)	68 (12.2)	72 (17.0)	
Transfer	332 (12.8)	120 (22.8)	113 (20.2)	118 (27.8)	
Missing information	160 (6.2)	20 (3.8)	19 (3.4)	11 (2.6)	
Operations					<0.0001
CABG	414 (16.0)	183 (34.7)	330 (59.0)	257 (60.6)	
Valve	1,739 (67.3)	229 (43.4)	146 (26.1)	95 (22.4)	
CABG and valve	296 (11.5)	96 (18.2)	73 (13.1)	60 (14.1)	
Thoracic aneurysm	69 (2.7)	12 (2.3)	5 (0.9)	5 (1.2)	
Other operation	66 (2.5)	7 (1.3)	5 (0.9)	7 (1.6)	
Comorbidities					
Hypertension	1,546 (59.8)	446 (84.6)	499 (89.3)	370 (87.3)	<0.0001
Valvular disease	2,066 (79.9)	348 (66.0)	268 (47.9)	192 (45.3)	<0.0001
Congestive heart failure	859 (33.2)	251 (47.6)	214 (38.3)	209 (49.3)	<0.0001
Peripheral vascular disease	484 (18.7)	141 (26.8)	103 (18.4)	115 (27.1)	<0.0001
Pulmonary circulation disorder	485 (18.8)	135 (25.6)	73 (13.1)	88 (20.7)	<0.0001
Renal failure	278 (10.8)	138 (26.2)	98 (17.5)	184 (43.4)	<0.0001
Chronic pulmonary disease	351 (13.6)	121 (23.0)	85 (15.2)	79 (18.6)	<0.0001
Obesity	263 (10.2)	93 (17.6)	135 (24.1)	120 (28.3)	<0.0001
Coagulopathy	159 (6.1)	32 (6.1)	17 (3.0)	17 (4.0)	0.0130
Weight loss	108 (4.2)	34 (6.4)	27 (4.8)	30 (7.1)	0.0188
Smoking					0.0951
No smoking	1,294 (50.1)	222 (42.1)	254 (45.4)	199 (46.9)	
Former smoker	947 (36.6)	202 (38.3)	215 (38.5)	162 (38.2)	
Current smoker	225 (8.7)	75 (14.2)	71 (12.7)	41 (9.7)	
Unknown	118 (4.6)	28 (5.3)	19 (3.4)	22 (5.2)	
HbA_{1c}* (%)	5.6, 5.7 (5.4–5.9)	65, 6.1 (5.6–6.9)	7.5, 7.2 (6.5–8.1)	8.5, 8.0 (6.9–9.4)	<0.0001
HbA_{1c}* (mmol/mol)	38, 39 (36–41)	48, 43 (38–52)	58, 55 (48–65)	69, 64 (52–79)	<0.0001

Results are shown as mean, median (interquartile range) or *n* (%). Four patients with DM did not have information on prior medication use and are not included in this table. *For HbA_{1c}: *n* = 811 in NODM, 244 in DMNT, 312 in DMOM, and 266 in DMIT.

average lactate. When the patient population was divided into quartiles of time-weighted average lactate, the patients with DM and NODM both demonstrated worsening outcomes at progressively higher lactate concentration quartiles (Fig. 2). When the cohort was divided into quartiles of HGI, the percentage of patients who had pulmonary failure, infection, died in the hospital, or had longer LOS increased progressively from the lowest to the highest quartile of HGI, but only in patients with NODM. On the contrary, in patients with DM, pulmonary failure demonstrated a decreasing trend, infection and death did not show a significant correlation with HGI quartiles, and postoperative LOS was slightly decreased.

We evaluated postoperative lactate levels (time-weighted average) and postoperative glucose levels (time-weighted average or HGI) as potential risk factors for mortality, pulmonary failure, and infection in multivariable analysis (see Supplementary Tables 1–3). We identified a three-way interaction among glucose, lactate, and DM in predicting mortality and pulmonary failure (Supplementary Tables 1 and 2). In the presence of an average blood glucose concentration, mortality increased with increasing lactate. This increase was reduced with increasing glucose levels in DM but not in NODM; for example, an increase in lactate of 1 mmol/L at a time-weighted average glucose of 124 mg/dL (the mean value of the cohort) was associated with increased mortality in NODM (hazard ratio [HR] 2.33; 95% CI 1.964, 2.751) and

Table 2—Glucose control parameters during the first 48 h after surgery

	NODM	DMNT	DMOM	DMIT	*P* value
Glucose*					
Glucose measurements per patient (*n*)	26.4, 26.0 (23–30)	28.4, 28.0 (24–32)	27.6, 27.0 (24–31)	28.9, 28.0 (25–33)	<0.0001
Time-weighted average (mg/dL)	119, 118 (112–126)	126, 123 (115–133)	135, 133 (122–145)	139, 135 (123–152)	<0.0001
CV	20.7, 19.6 (15.7–24.6)	24.2, 23.3 (18.6–28.6)	25.8, 24.9 (20.6–30.5)	28.2, 27.7 (23.1–32.4)	<0.0001
Patients with hyperglycemia	672 (26.0)	245 (46.5)	351 (62.8)	313 (73.8)	<0.0001
Patients with hypoglycemia	162 (6.3)	48 (9.1)	49 (8.8)	46 (10.8)	0.0012
Lactate†					
Lactate measurements per patient (*n*)	19.1, 18.0 (14–23)	21.0, 21.0 (16–25)	19.4, 18.0 (15–24)	20.7, 21.0 (16–25)	<0.0001
Time-weighted average (mmol/L)	1.8, 1.5 (1.1–2.2)	1.8, 1.5 (1.1–2.1)	1.5, 1.3 (1.1–1.8)	1.5, 1.3 (1.1–1.7)	<0.0001
CV	45.3, 42.8 (31.3–57.6)	46.9, 43.8 (32.1–59.0)	45.5, 41.6 (31.9–56.1)	41.8, 39.9 (28.9–53.5)	0.001
Patients with hyperlactatemia	946 (36.6)	193 (36.6)	149 (26.6)	95 (22.4)	<0.0001
(Hyperlactatemia among patients with hyperglycemia)					
All operations	440 (65.5)	117 (47.8)	110 (31.3)	83 (26.5)	<0.0001
CABG	39 (52.0)	25 (30.1)	47 (23.0)	35 (17.6)	<0.0001
Valve	311 (65.9)	53 (53.0)	34 (38.2)	25 (37.9)	<0.0001
CABG and valve	63 (77.8)	31 (60.8)	25 (48.1)	21 (50)	0.0015
Thoracic aortic aneurysm	16 (66.7)	5 (62.5)	3 (100)	2 (66.7)	0.8671
Other	11 (55)	3 (100)	1 (33.3)	0 (0)	0.0882
(Hyperlactatemia among patients without hyperglycemia)					
All operations	506 (26.5)	76 (26.9)	39 (18.7)	12 (10.8)	<0.0001
Mortality‡	42 (1.6)	15 (2.8)	7 (1.2)	6 (1.4)	0.1664

Results are shown as mean, median (interquartile range) or *n* (%). Comparisons of frequencies were conducted using the χ^2 test. Comparisons for continuous variables were conducted using the Kruskal-Wallis nonparametric test. The *P* values refer to the null hypothesis of equivalency across groups, with the alternative hypothesis that at least one of the groups is different. Patients with only one glucose or lactate measurement were not included. *$n_{(NODM)}$ = 2,584, $n_{(DMNT)}$ = 526, $n_{(DMOM)}$ = 558, and $n_{(DMIT)}$ = 424. †$n_{(NODM)}$ = 2,580, $n_{(DMNT)}$ = 525, $n_{(DMOM)}$ = 557, and $n_{(DMIT)}$ = 423. ‡Among the patients who died: seven patients (four NODM and three DMOM) died within 48 h of surgery; four patients with DM died without data on medication history (not included in the table). The difference in mortality between NODM (42 [1.6%]) and DM (32 [2.1%]), including these 4 patients without medication history, was not significant (*P* = 0.2573).

in DM (HR 2.32, 95% CI 1.785, 2.901). However, at a glucose time-weighted average of 180 mg/dL, the increase in mortality was no longer significant in DM (HR 1.28; 95% CI 0.809, 1.775) but remained significant in NODM (HR 3.16; 95% CI 1.754, 5.068). Moreover the risk of mortality associated with increased lactate levels decreased over time (HR 0.98 per day; 95% CI 0.972, 0.991). In a similar manner, increased pulmonary failure was associated with increasing lactate. This effect lessened with increasingly higher levels of time-weighted average glucose in DM but not in NODM. Finally, DM and lactate were independently associated with increased infection, whereas time-weighted average glucose was associated with reduced infection (Supplementary Table 3). HGI gave equivalent results to those obtained by using the glucose time-weighted average for mortality and pulmonary failure and was not a significant predictor for infection (not shown).

CONCLUSIONS

Extreme metabolic responses to surgical stress, such as hyperglycemia and hyperlactatemia, have been associated with worse outcomes after major operations and in critical illness. In patients with DM, however, a large body of literature has shown that the association between hyperglycemia and adverse outcomes is profoundly reduced (12–14,24). The reasons underlying this phenomenon and the potential implications for glycemic management remain uncertain. In this study, we investigated the relationship between glucose and blood lactate levels after cardiac surgery and tested the hypothesis that DM alters the association of hyperlactatemia with adverse outcomes. We found that:

1. The stress-induced increase in lactate levels is strongly attenuated in patients with DM, especially among patients with DMIT.
2. Lactate levels are associated with glucose levels and glycemic variability in patients with NODM, this association is dramatically reduced in patients with DM, and the relationship of the lactate time-weighted average to the glucose time-weighted average by DM status did not change in an exploratory analysis stratifying patients by insulin treatment (data not shown).
3. Finally, increasing blood lactate is associated with increasing mortality, and this association is modified by glucose levels and DM in a three-way interaction.

Lactate is a by-product of glycolysis that, together with glucose, plays a major role in the bioenergetics of the stress response (3). The etiology of increased lactate levels after cardiac surgery is likely to be multifactorial, and at present the mechanisms involved are not completely understood. Results from several studies suggest that elevated blood lactate may be an indication of inadequate tissue perfusion (25). A reduction in oxygen delivery, due to hypoperfusion or reduced postoperative cardiac performance, would inhibit oxidative phosphorylation, in turn blocking the entry of pyruvate into the tricarboxylic acid cycle and increasing its conversion into lactate (6). Alternatively, catecholamine and inflammatory mediators, released in response to surgical stress, may stimulate glycolysis and increase lactate production under normal

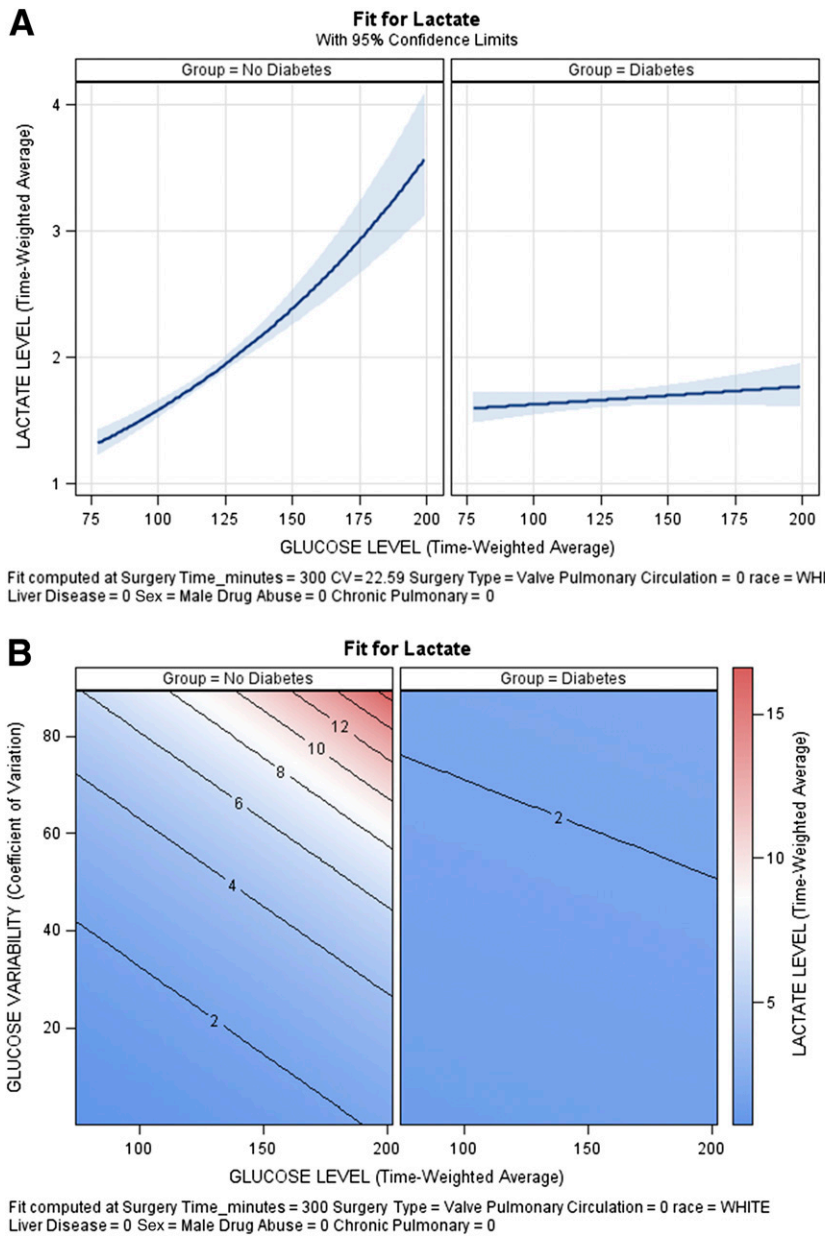

Figure 1—Relationship between blood glucose levels and blood lactate levels in patients with DM and with NODM. Association between lactate and glucose time-weighted averages shown alone (*A*) and together with glycemic variability (*B*). The association was modeled using generalized linear regression. The final model included type of surgery, duration of surgery, pulmonary circulation disorder, race, liver disease, drug abuse, sex, and chronic pulmonary disease. Glucose and lactate parameters (time-weighted averages and CV for glucose) were obtained from measurements during the first 48 h after surgery. The graphs in *A* and *B* present the relationship for the "average" patient, where surgery duration is 300 min, type of surgery is valve surgery, race is white, sex is male, and CV is 22.59 (*A*) or variable (*B*), and there is no pulmonary circulation disorder, liver disease, drug abuse, or chronic pulmonary disease. *B*: The lines and values positioned on the contour plot are the lactate time-weighted averages that correspond to the different colors, as indicated in the color legend (bar on the right). *C*: Relationship of peak lactate with hyperglycemia (>180 mg/dL) and hypoglycemia (<70 mg/dL). The *P* values are shown for within-group comparisons of mean peak lactate (with dysglycemia vs. without dysglycemia). The relationship reported in the text of peak lactate with the patient group and hyperglycemia (or hypoglycemia) was analyzed by generalized linear regression using the two following sets of covariates: hyperglycemia, patient group, and their interaction; and hypoglycemia, patient group, and their interaction. All parameters were assessed during the first 48 h after surgery. *D*: Changes in lactate levels over time in patients with "high" or "low" glucose levels at surgery. With the exception of the preoperative period (Preop), which is represented by a single measure, all other points are time-weighted averages of all the measurements taken during the specified period (e.g., Intraop: measurements taken during surgery; 6 h: measurements taken during the first 6 h after surgery, etc.). "Low" (dashed lines): time-weighted average glucose at surgery below the median. "High" (solid lines): time-weighted average glucose at surgery above the median. Error bars (*C*, *D*) indicate 95% CI.

aerobic conditions (3). In the context of cardiac surgery, it is conceivable that anaerobic metabolism from a local oxygen deficit and a state of accelerated glycolysis, without hypoxia, might simultaneously contribute to the transient increase in lactate concentration that starts during surgery and subsides after ~1 day (Fig. 1*D*).

As a strong anion, elevated lactate concentration can cause lactic acidosis, which is generally defined by lactate concentration >5 mmol/L associated with metabolic acidosis (blood pH <7.35) (26). Studies have consistently shown that the level of fasting lactate in the blood is higher in individuals with DM than in those with NODM, possibly resulting from a decreased aerobic-oxidative capacity associated with mitochondrial dysfunction, decreased activity of the pyruvate dehydrogenase complex, or reduced tissue microcirculation (6,27,28). Despite their apparent predisposition to develop lactic acidosis, however, the incidence of this disorder is very low in patients with DM (the upper limit is 2.4/100,000 patient-years) (29).

In our study, we used the surgery duration as a surrogate marker of the duration of cardiopulmonary bypass and found that increased surgery duration was a risk factor for increased lactate levels. Previous studies examining blood lactate in cardiac surgery have shown that increased lactate levels are associated with an increased duration of cardiopulmonary bypass and a longer time on the ventilator (1,9,30). The decrease in stress hyperlactatemia we observed in patients with DM was not likely determined by any of these factors. First, patients with DM would need to spend a significantly shorter time on cardiopulmonary bypass compared with patients with NODM to explain our results, a hypothesis that counters clinical experience. Second, the prolonged ventilation that was reported to be associated with hyperlactatemia (45 h) and the time on ventilation associated with normal blood lactate (12 h) both exceeded the time when peak lactate occurred, which was within the first 10 h after surgery (consistent with our findings) (1).

The effect of DM on the relationship between hyperglycemia and lactate can be potentially explained by considering the hyperglycemic patient with DM as being in a state of relative insulin

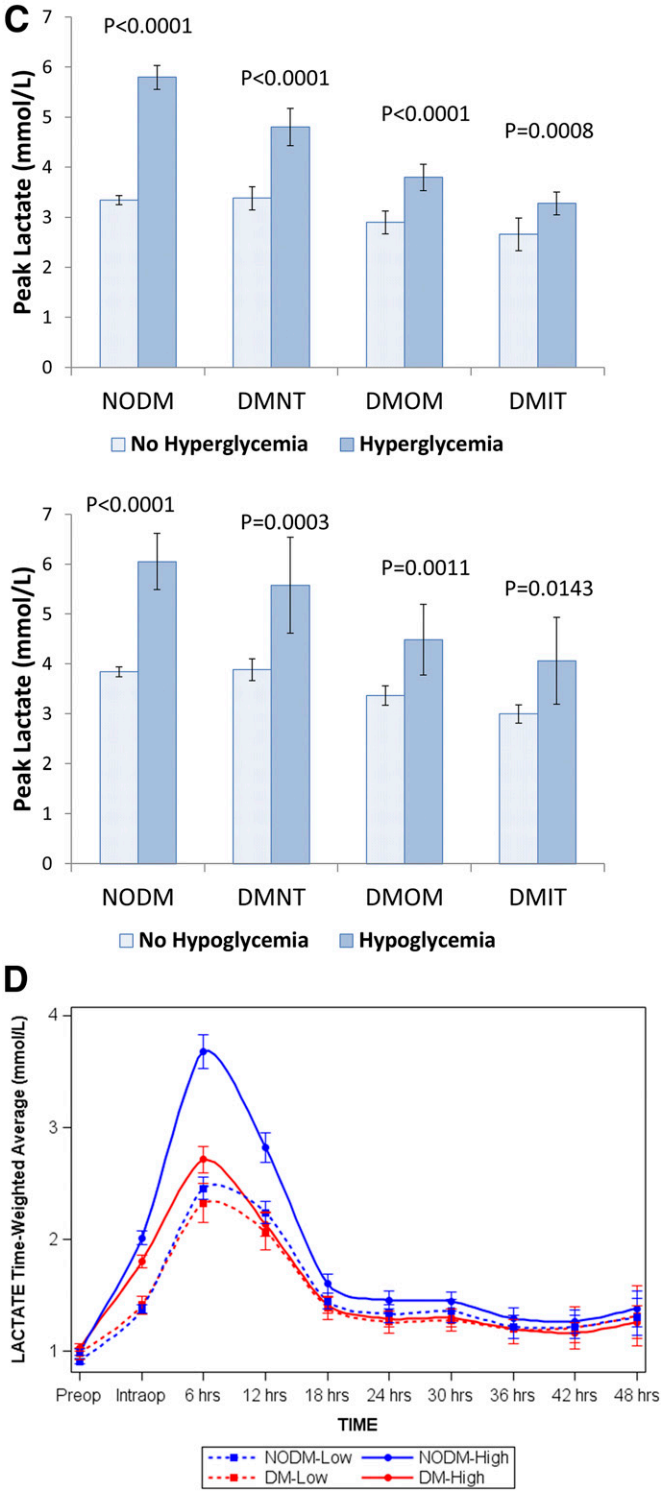

Figure 1—*Continued.*

insufficiency. Insulin is an important positive regulator of glycolysis because it controls glucose uptake and promotes the activation and gene expression of key glycolytic enzymes (31). In a state of relative insulin insufficiency and stress hyperglycemia, there might ultimately be a decrease in the conversion of glucose to pyruvate and, therefore, a decrease in lactate production. Indeed, the capacity to increase plasma lactate concentration during hyperinsulinemic-euglycemic clamps is impaired in patients with type 2 DM compared with healthy subjects (32,33). A reduced increase in the plasma lactate in response to a glucose load and hyperinsulinemia has also been described in insulin-resistant obese individuals compared with healthy lean individuals (34). On one hand, the reduced increase of lactate levels in the presence of hyperglycemia, therefore, might be the result of a decreased activation of the glycolytic pathway in patients with DM compared with patients with NODM. On the other hand, insulin is also responsible for the inhibition of gluconeogenesis, whereby lactate is used as a precursor for the synthesis of glucose within liver and kidneys through the Cori cycle (35). In a state of relative insulin deficiency, the lack of gluconeogenesis inhibition might increase the clearance of lactate during stress-induced hyperlactatemia, resulting in a lower level of lactate in patients with DM.

The uncoupling of postoperative hyperglycemia and hyperlactatemia provides a possible explanation of the blunted association between hyperglycemia and adverse outcomes in patients with DM compared with patients with NODM. Previous studies have shown that lactate is a better predictor of mortality than hyperglycemia and that the independent relationship existing between hyperglycemia and increased mortality ceased once lactate levels were taken into account (10,11). In this study, increased lactate levels, but not glucose levels, retained the ability to prognosticate morbidity and mortality in a dose-dependent fashion in patients with DM (Fig. 2).

The association of increasing lactate levels with morbidity and mortality may, to some extent, be associated with its acidifying effect, which causes cellular dysfunction and hemodynamic changes (7). Elevated lactate levels, however, can also occur without accompanying increases in systemic acidity; therefore, the mechanisms underlying the observed dose response of lactate on worse outcomes and its potential causal role have yet to be determined.

From a clinical perspective, lactate has been increasingly used in sepsis management (36). There are data to support lactate clearance as a guide for early recovery from sepsis (37,38) and, potentially, a marker for later recovery as well (39). Elevated lactate levels in sepsis prompt the provider to enact aggressive resuscitation of the patient (36). Further, because of mounting evidence that hyperlactatemia in the first 24 h is associated

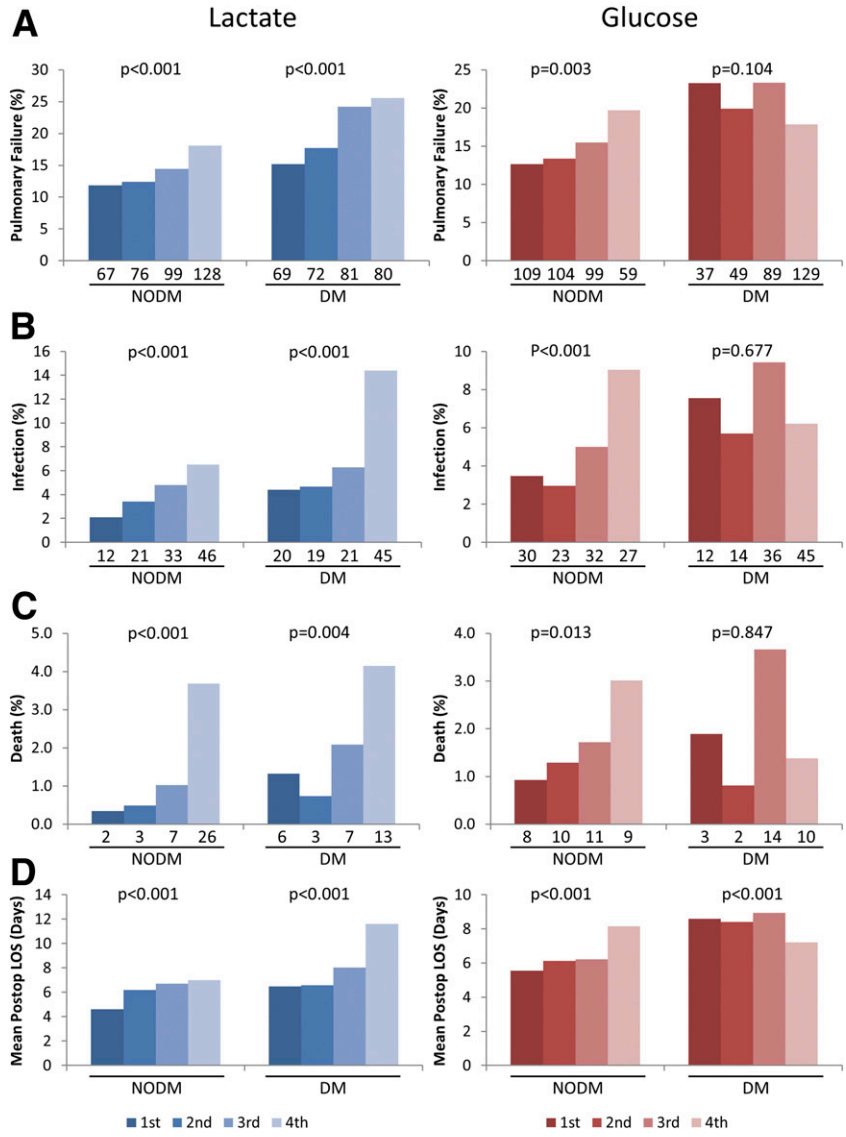

Figure 2—Patients with pulmonary failure (*A*), infection (*B*), and in-hospital death (*C*), and mean postoperative LOS (*D*) in patients with DM and NODM by quartiles of the time-weighted average lactate (left) and by quartiles of the HGI (right). The numbers below the bars indicate patients with the event (*A*–*C*) in each quartile. Number of subjects per quartile of time-weighted average lactate were 1st: n_{NODM} = 567, n_{DM} = 453; 2nd: n_{NODM} = 614, n_{DM} = 406; 3rd: n_{NODM} = 686, n_{DM} = 335; and 4th: n_{NODM} = 707, n_{DM} = 313. Number of subjects per quartile of HGI were 1st: n_{NODM} = 863, n_{DM} = 159; 2nd: n_{NODM} = 776, n_{DM} = 246; 3rd: n_{NODM} = 640, n_{DM} = 382; and 4th: n_{NODM} = 299, n_{DM} = 723. Glucose and lactate parameters were obtained from measurements taken during the first 48 h after surgery. *P* values in *A*–*C* were computed using the Cochran-Mantel-Haenszel test for trend. The *P* value for the association with postoperative LOS was computed from generalized linear regression by using LOS as the dependent variable and HGI or time-weighted average lactate as the independent variable. Postoperative LOS was calculated starting 48 h after surgery (day 2 after surgery = day 0). This analysis excluded patients who died within 48 h after surgery (n = 7), were discharged within 48 h (n = 2), or had only one lactate measurement (n = 8).

with increased morbidity and mortality, there is consideration of the potential usefulness of lactate clearance–directed therapy (40).

Given these findings, it is worthwhile to consider whether insulin, beyond fluid resuscitation, vasopressors, and antibiotic therapy, can be used as a component of goal-directed lactate clearance therapy rather than purely for glycemic control. Our data would also suggest that the avoidance of hyperglycemia in patients without a prior diagnosis of DM could potentially have an effect on lactate levels and, ultimately, outcomes, more so than in patients with DM. Other groups have also observed the larger benefit in outcomes derived in patients with NODM with intensive insulin therapy (15–17).

The concept of glycemic control in critically ill patients has been examined and discussed extensively during the last two decades. Multiple, large-scale clinical trials examining the effect of intensive insulin therapy in a variety of clinical settings have yielded mixed results. Methodological differences, including variable glucose targets, glucose control algorithms, accuracy of glucose meters, and rates of hypoglycemia, are all potential reasons for the differences in outcomes from the randomized controlled trials. As the targets for glycemic control in critical illness are still debated, given our findings regarding the association between hyperglycemia, DM, and lactate levels, an area for future investigation would be the utility of insulin in lactate clearance–directed therapy and its effect on clinical outcomes.

Limitations

The chief limitation of this study is in the retrospective nature of the analysis and that the data originated from a single center, which might affect the generalizability of the findings. Our findings, however, are consistent with results from our previous multicenter study (12). Moreover, the size and diversity of our cohort, with patients of different races/ethnicities, socioeconomic statuses, and comorbid conditions, strengthens the generalizability of our findings. Second, complications and comorbidities, including DM, were identified through ICD-9 codes. This method is prone to miscoding and misclassification. However, it is highly unlikely that errors in coding might have differentially biased the results among the patients in our different subgroups. Third, we recognize that because DM treatment is often tailored based on comorbidities, by grouping patients according to antecedent DM treatment, there may be some unaccounted for differences between the groups. However, several important factors were controlled for in our multivariable analyses, including demographics, type of surgery and its duration, admission modality, smoking status, type of insurance, and comorbidities from the Elixhauser comorbidity system. Finally, we did not have information on disease duration or microvascular complications, and HbA_{1c} information was available only for a subset of the patients. Our classification, based on prior

medication use, does not fully reflect actual differences in the DM disease severity or its pathophysiological heterogeneity, and for the patients where no history of glucose-lowering medication was reported (DMNT), we do not know whether this resulted from effective lifestyle modifications, early diagnosis of DM, admission modality, or discontinuation of medications due to improved control of DM or access to care issues.

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