The Association of Preoperative Glycemic Control, Intraoperative Insulin Sensitivity, and Outcomes after Cardiac Surgery

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Context: The impairment of insulin sensitivity, a marker of surgical stress, is important for outcomes.

Objective: The aim was to assess the association between the quality of preoperative glycemic control, intraoperative insulin sensitivity, and adverse events after cardiac surgery.

Design and Setting: We conducted a prospective cohort study at a tertiary care hospital.

Subjects: Nondiabetic and diabetic patients scheduled for elective cardiac surgery were included in the study. Based on their glycosylated hemoglobin A (HbA_{1c}), diabetic patients were allocated to a group with good (HbA_{1c} <6.5%) or poor (HbA_{1c} >6.5%) glycemic control.

Intervention: We used the hyperinsulinemic-normoglycemic clamp technique.

Main Outcome Measures: The primary outcome was insulin sensitivity measurement. Secondary outcomes were major complications within 30 d after surgery including mortality, myocardial failure, stroke, dialysis, and severe infection (severe sepsis, pneumonia, deep sternal wound infection). Other outcomes included minor infections, blood product transfusions, and the length of intensive care unit and hospital stay.

Results: A total of 143 nondiabetic and 130 diabetic patients were studied. In diabetic patients, a negative correlation ($r = -0.527$; $P < 0.001$) was observed between HbA_{1c} and intraoperative insulin sensitivity. Diabetic patients with poor glycemic control had a greater incidence of major complications ($P = 0.010$) and minor infections ($P = 0.006$). They received more blood products and spent more time in the intensive care unit ($P = 0.030$) and the hospital ($P < 0.001$) than nondiabetic patients. For each 1 $mg \cdot kg^{-1} \cdot min^{-1}$ decrease in insulin sensitivity, the incidence of major complications increased ($P = 0.004$).

Conclusions: In diabetic patients, HbA_{1c} levels predict insulin sensitivity during surgery and possibly outcome. Intraoperative insulin resistance is associated with an increased risk of complications, independent of the patient's diabetic state. **(*J Clin Endocrinol Metab* 95: 4338–4344, 2010)**

Major surgical tissue trauma leads to stereotypical alterations in glucose metabolism, including stimulated glucose production and impaired glucose utilization, resulting in hyperglycemia (1). Much of this metabolic derangement can be explained by specific neuroendocrine changes such as increased circulating concentrations of cortisol, glucagon, and catecholamines (1, 2). These hormones affect glucose homeostasis, either directly or indi-

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Abbreviations: CABG, Coronary artery bypass grafting; CPB, cardiopulmonary bypass; HbA_{1c}, glycosylated hemoglobin A; ICU, intensive care unit; OR, odds ratio.

rectly, by inhibiting insulin secretion and/or counteracting its peripheral action, causing impairment of tissue insulin sensitivity, the so-called "diabetes of the injury" (3, 4). The extent of insulin resistance during surgery depends on the intensity of trauma, suggesting that insulin resistance is a marker of surgical stress with potential relevance for clinical outcome (4, 5). Considering the fact that even moderate hyperglycemia significantly contributes to morbidity and mortality after cardiac surgery, predicting the extent of perioperative insulin sensitivity has potentially important clinical implications (6–9).

Plasma glycosylated hemoglobin A (HbA_{1c}) is an established indicator of blood glucose control during the previous 3 to 4 months (10). Although the relationship between preoperative plasma HbA_{1c} levels and intraoperative insulin sensitivity is unknown, recent evidence suggests a prognostic value of HbA_{1c} regarding outcomes after major surgical interventions (11–14).

The purpose of this study was to test the hypothesis that the quality of preoperative glycemic control as assessed by plasma HbA_{1c} predicts insulin sensitivity during cardiac surgery. We also examined whether poor glycemic control before and insulin sensitivity during surgery are associated with an increased risk of postoperative complications.

Subjects and Methods

This study was conducted according to the Declaration of Helsinki. With approval from the McGill University Health Center Research Ethics Board, we approached patients scheduled for elective coronary artery bypass grafting (CABG), valve procedure, or a combination of both between May 2008 and April 2009 at the Royal Victoria Hospital. Patients scheduled for off-pump CABG, emergency procedures, or procedures with anticipated deep hypothermic circulatory arrest were excluded. We also excluded patients who were on hemodialysis or had troponin I levels of at least 0.5 ng $\cdot$ liter^{-1}.

Patients not known for diabetes presenting with blood glucose levels greater than 7.0 mmol/liter or HbA_{1c} greater than 6.0% also were not eligible. Only patients with a confirmed diagnosis of type 2 diabetes mellitus and receiving treatment (oral antihyperglycemic agents, or insulin) were considered diabetic. Based on their HbA_{1c} concentrations, diabetics were allocated to a group with good (HbA_{1c} <6.5%) or poor (HbA_{1c} >6.5%) glycemic control (15).

Patients received standardized iv anesthesia using sufentanil and midazolam supplemented with inhaled sevoflurane. During cardiopulmonary bypass (CPB), mean arterial pressure was maintained between 50 and 70 mm Hg. Moderate hemodilution (hematocrit 20–25%) and mild hypothermia (34 C) were tolerated during CPB.

Insulin sensitivity was assessed by the hyperinsulinemic-normoglycemic clamp technique (16, 17). Before induction of anesthesia, insulin (Humulin R; Eli Lilly & Company, Indianapolis, IN) was administered iv at 5 mU $\cdot$ kg^{-1} $\cdot$ min^{-1}. Approximately 10 min after starting the insulin infusion, and when the blood glucose was less than 6.1 mmol $\cdot$ liter^{-1}, dextrose 20% supplemented with phosphate (30 mmol $\cdot$ liter^{-1}) was administered. Arterial blood glucose concentrations were determined every 5 min, and the dextrose infusion was adjusted to maintain blood glucose at 5.0 mmol $\cdot$ liter^{-1} (90 mg $\cdot$ dl^{-1}). The dextrose infusion rate during steady-state conditions, before and toward the end of CPB, was used as an indicator of insulin sensitivity. We assumed steady-state conditions if the coefficient of variation of five subsequent dextrose infusion rates was less than 5%.

At the end of surgery (skin closure), the insulin infusion was stopped. The dextrose infusion was maintained for 2 h to avoid hypoglycemia. In the intensive care unit (ICU), following the routine guidelines for this patient population at the Royal Victoria Hospital, an insulin sliding scale was applied aiming at a blood glucose between 4.0 and 8.0 mmol $\cdot$ liter^{-1}. Blood glucose was measured every 1 to 2 h, and the average blood glucose during the first 24 h after surgery was calculated.

Complications were assessed 30 d after surgery. Major complications included all-cause mortality, myocardial failure (cardiac index <1.8 liter $\cdot$ min^{-1} $\cdot$ m^{-2} and mixed venous saturation <55%, despite adequate fluid replacement, and high-dose inotropic support requiring either intraaortic balloon pump, right and/or left ventricular assist device, and/or extracorporeal mechanical oxygenation after separation from CPB), stroke (new focal or global neurological deficit confirmed by clinical findings and computed tomographic scan), dialysis, and serious infection (severe sepsis, pneumonia requiring mechanical ventilation, deep sternal wound infection) (18). Other complications included minor infections such as pneumonia not requiring mechanical ventilation, superficial wound and urinary tract infection, and blood product transfusions. We also documented the peak postoperative creatinine plasma concentration, the duration of intubation, as well as length of ICU and hospital stay.

Patient demographics, blood glucose concentrations, and insulin sensitivity were compared using one-way ANOVA with Tukey-Kramer multiple comparisons posttest or χ^2 test for categorical variables. The paired t test was used for comparisons within groups regarding changes in intraoperative insulin sensitivity. Stepwise multiple regression analysis was performed between intraoperative insulin sensitivity and preoperative patient variables including age, body weight, body mass index, HbA_{1c} concentration, fasting blood glucose concentration, mean blood pressure, and plasma creatinine.

The difference in the incidence of complications was analyzed by the Kruskal-Wallis test with Steel-Dwass multiple comparisons posttest or χ^2 test for categorical variables. The Pearson correlation coefficient and linear regression were used to describe the association between plasma HbA_{1c} and insulin sensitivity as expressed by the dextrose infusion rate during steady-state conditions toward the end of CPB. A logistic regression model assessed the relationship between insulin sensitivity and adverse outcomes while adjusting for potential confounders. Variables in Table 1 were put into the multivariable model. Two-sided P values less than 0.05 were considered statistically significant.

Sample size was calculated on the basis of the primary study hypothesis assuming a negative correlation between plasma HbA_{1c} and insulin sensitivity during CPB. A sample size of 120 achieves 80% power to detect a slope of 0.5 under the alternative hypothesis when the SD of the HbA_{1c} is 2, the SD of the dextrose infusion rate is 4, and the significance level is 0.05.

TABLE 1. Demographics

	Non-DM	DM	
		HbA_{1c} <6.5%	HbA_{1c} >6.5%
n	143	61	69
Age (yr)	65 ± 14	68 ± 9	66 ± 10
Body mass index (kg/m^2)	27.5 ± 5.1	28.5 ± 5.7	29.2 ± 5.9
Gender (males/females)	109/34	43/18	48/21
HbA_{1c} (%)	5.4 ± 0.3	6.1 ± 0.3[c]	7.6 ± 0.9[a,b]
Parsonnet score	17 ± 11	19 ± 10	18 ± 11
Euro score	3.0 ± 1.8	3.2 ± 1.5	3.1 ± 1.8
Ejection fraction (%)	52 ± 11	51 ± 12	50 ± 12
ACE inhibitors	79 (55.2)	36 (59.0)	42 (61.0)
β-Blockers	98 (68.5)	47 (77.0)	48 (70.0)
Ca channel-blockers	34 (23.8)	21 (34.4)	20 (29.0)
Statins	98 (68.5)	48 (78.7)	54 (78.3)
Corticosteroids	6 (4.2)	2 (3.3)	3 (4.3)
Insulin	0	14 (23.0)	19 (27.5)
Thiazolidinediones	0	3 (4.9)	5 (7.2)
Biguanides	0	31 (50.8)	35 (50.7)
Sulfonylureas and meglitinides	0	14 (23.0)	16 (23.2)
Hematocrit (%)	39.0 ± 5.5	38.7 ± 5.0	38.5 ± 5.6
Creatinine (μmol/liter)	93 ± 19	90 ± 21	94 ± 23
Fasting blood glucose (mmol/liter)	5.6 ± 0.8	6.6 ± 1.6[c]	8.5 ± 2.1[a,b]
Mean blood pressure (mm Hg)	84 ± 15	85 ± 14	85 ± 17
CABG	86 (60.1)	35 (57.3)	43 (62.3)
Valve	29 (20.3)	12 (19.7)	12 (17.4)
CABG and valve	28 (19.6)	14 (23.0)	14 (20.3)
Aortic cross clamp time (min)	85 ± 33	84 ± 28	86 ± 31
CPB time (min)	104 ± 42	107 ± 45	108 ± 43
Minimum temperature during CPB (C)	33.7 ± 1.1	33.9 ± 1.5	34.0 ± 1.4
Duration of surgery (min)	218 ± 63	217 ± 55	211 ± 56

Data are expressed as mean ± SD or number (percent). DM, Diabetes mellitus; ACE, angiotensin-converting enzyme.

[a] $P < 0.05$ non-DM *vs.* DM HbA_{1c} >6.5%.

[b] $P < 0.05$ DM HbA_{1c} <6.5% *vs.* DM HbA_{1c} >6.5%.

[c] $P < 0.05$ non-DM *vs.* DM HbA_{1c} <6.5%.

Results

We studied 143 nondiabetic and 130 diabetic patients. Patient demographics were similar in all groups except for plasma HbA_{1c} and fasting blood glucose concentration, which were increased in the two diabetic groups ($P < 0.001$; Table 1).

In all patients, insulin sensitivity decreased during CPB when compared with before CPB ($P < 0.001$). Diabetic patients with poor preoperative glycemic control showed a greater degree of insulin resistance before separation from CPB (Fig. 1; $P < 0.001$) and an increased blood glucose concentration in the ICU (see Table 3; $P < 0.001$) when compared with well-controlled diabetic and nondiabetic patients.

In patients with diabetes, a weak but significant negative correlation (Fig. 2; $r = -0.527$; $P < 0.001$) was observed between preoperative HbA_{1c} concentrations and insulin sensitivity before separation from CPB.

This relationship can be described as insulin sensitivity $= -0.554 \cdot [HbA_{1c}] + 6.238$.

Furthermore, intraoperative insulin sensitivity negatively correlated with body mass index (Table 2).

In nondiabetic patients, negative correlations were observed between insulin sensitivity and body weight, fasting blood glucose, and plasma creatinine (Table 2).

The incidence of complications in nondiabetic patients and diabetic patients with good preoperative glycemic control was similar. The peak creatinine plasma concentration after surgery was higher in well-controlled diabetics than in the nondiabetic study group ($P = 0.042$). The number of patients who suffered a major complication was significantly increased in diabetics with poor preoperative glycemic control when compared with normals ($P = 0.010$; Table 3). Diabetic patients showing a HbA_{1c} concentration greater than 6.5% had a greater incidence of severe ($P = 0.035$) and minor infections ($P = 0.006$), received more blood products (packed red blood cells, $P = 0.046$; fresh frozen plasma, $P = 0.035$; platelets, $P < 0.001$), had a higher peak creatinine level ($P = 0.011$), and spent more time in the ICU ($P = 0.030$) and the hospital ($P < 0.001$) than nondiabetics (Table 3). Poor preoperative glycemic control was associated with a

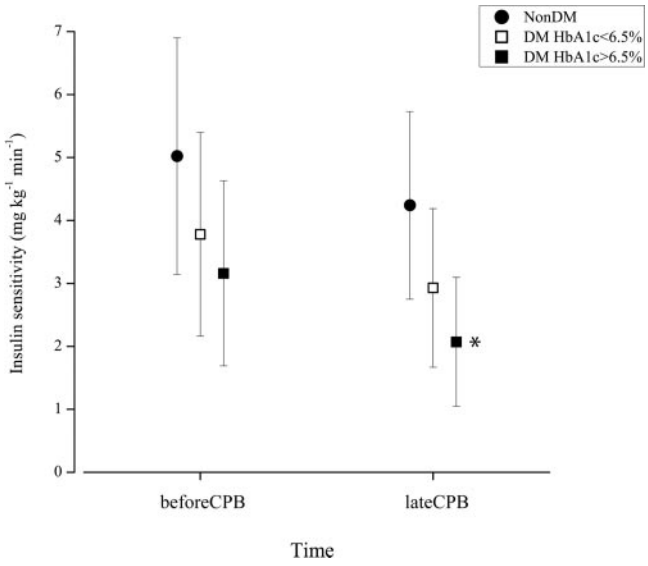

FIG. 1. Insulin sensitivity in nondiabetic and diabetic patients before and during late CPB (DM HbA_{1c} <6.5% = good glycemic control group; DM HbA_{1c} >6.5% = poor glycemic control group). Data are expressed as means ± SD. The dextrose infusion rate ($mg \cdot kg^{-1} \cdot min^{-1}$) during steady-state conditions was used as an indicator of insulin sensitivity. Insulin sensitivity during late CPB in diabetic patients with poor preoperative glycemic control was lower than in nondiabetic patients and diabetic patients with good glycemic control. *, $P < 0.01$. DM, Diabetes mellitus; NonDM, non diabetes mellitus; beforeCPB, before CPB; lateCPB, before separation from CPB.

greater incidence of minor infections when compared with diabetic patients with good glycemic control ($P = 0.034$; Table 3). In particular, the rate of superficial wound infections was increased.

Independent of the presence of diabetes mellitus, for each 1 $mg \cdot kg^{-1} \cdot min^{-1}$ decrease in insulin sensitivity, we observed an increased incidence of major complications [odds ratio (OR) = 2.23; $P = 0.004$] and severe (OR = 4.98; $P = 0.010$) and minor infections (OR = 1.97; $P = 0.003$) (Table 4).

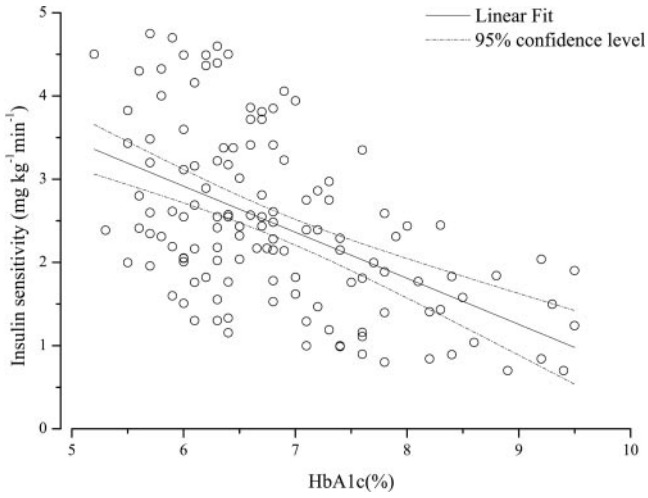

FIG. 2. Association between preoperative HbA_{1c} levels (%) and insulin sensitivity during late CPB in diabetic patients. The dextrose infusion rate ($mg \cdot kg^{-1} \cdot min^{-1}$) during steady-state conditions was used as an indicator of insulin sensitivity. A significant negative correlation was observed between the two variables (Pearson r = −0.527; $P < 0.001$). The linear regression of that relationship can be described as insulin sensitivity = $-0.554 \cdot [HbA_{1c}] + 6.238$.

TABLE 2. Stepwise multiple regression analysis

Variable	β-Coefficient	P
Nondiabetic patients		
Body weight (kg)	−0.301	<0.001
Fasting blood glucose (mmol/liter)	−0.180	0.015
Creatinine (μmol/liter)	0.142	0.049
Diabetic patients		
HbA_{1c} (%)	−0.494	<0.001
Body mass index (kg/m^2)	−0.222	0.004

Standardized β-coefficients of correlations between intraoperative insulin sensitivity and variables in nondiabetic and diabetic patients.

Discussion

The results of the present study demonstrate that in diabetic patients there is a weak, but significant, association between the quality of preoperative glycemic control and insulin sensitivity during cardiac surgery. Our results further suggest that insulin resistance during surgery, rather than the presence of diabetes mellitus, is associated with an increased risk of major complications.

At present, we are lacking methodological tools that would allow us to anticipate the degree of tissue insulin resistance and the hyperglycemic response during surgery (4). Taking into account the link between insulin resistance, hyperglycemia, and circulating HbA_{1c} concentrations, our finding that preoperative plasma HbA_{1c} levels predict intraoperative insulin resistance in diabetic patients is not unexpected. The patients' body mass index also was associated with insulin sensitivity. This association, being weaker than that with HbA_{1c}, however, was also observed in nondiabetic patients.

Although HbA_{1c} values have been widely investigated as an index of long-term blood glucose control and outcome predictors in diabetic patients, its predictive value in the surgical patient population has received little attention. In agreement with our findings demonstrating worse outcomes in the presence of increased HbA_{1c} values, a recent retrospective analysis showed that diabetic patients with elevated HbA_{1c} levels had an augmented adverse event rate and a higher 30-d mortality after cardiac procedures (12, 13). In another small cohort of presumably nondiabetic patients, elevated HbA_{1c} concentrations were associated with an increased risk of complications after vascular surgery (11). If it holds true that poor preoperative glycemic control adversely affects outcomes of diabetic patients, it remains to be studied whether the timely improvement of gly-

TABLE 3. Outcomes

		DM	
	Non-DM	HbA_{1c} <6.5%	HbA_{1c} >6.5%
n	143	61	69
Major complications	9 (6.2)	7 (11.5)	12 (17.4)[a]
Death	3 (2.1)	2 (3.3)	4 (5.8)
IABP	3 (2.1)	1 (1.6)	2 (2.9)
Dialysis	2 (1.4)	1 (1.6)	3 (4.3)
Stroke	1 (0.7)	2 (3.3)	1 (1.6)
Severe Infection	3 (2.1)	2 (3.3)	6 (8.7)[a]
Septic shock	1 (0.7)	0 (0)	1 (1.4)
Pneumonia (requiring ventilation)	1 (0.7)	1 (1.6)	3 (4.3)
DSWI	1 (0.7)	1 (1.6)	2 (2.9)
Other complications			
Minor infection	14 (9.8)	8 (13.1)	19 (27.5)[a,b]
Pneumonia (not requiring ventilation)	5 (3.5)	3 (4.9)	5 (7.2)
Superficial wound infection	6 (4.2)	5 (8.2)	8 (11.6)[a]
UTI	8 (5.6)	4 (6.6)	8 (11.6)
Blood transfusion			
RBC	88 (61.5)	41 (67.2)	52 (75.4)[a]
Units/patient	3.0 (2.0–5.0)	2.5 (2.0–5.0)	3.0 (2.0–6.0)
FFP	34 (23.8)	19 (31.1)	26 (37.7)[a]
Units/patient	3.0 (2.0–4.0)	2.9 (2.1–4.0)	4.0 (2.0–6.6)
Platelets	27 (18.9)	18 (29.5)	28 (40.6)[a]
Units/patient	5.8 (5.0–10.0)	6.0 (5.0–7.5)	6.4 (5.0–10.2)
Blood glucose in ICU (mmol/liter)	7.8 ± 1.4	8.3 ± 1.9	9.3 ± 2.9[a,b]
Creatinine (μmol/liter)	106 (90–131)	119 (100–144)[c]	135 (100–166)[a]
Intubation time (h)	7.8 (4.8–13.8)	8.8 (6.0–17.5)	9.3 (6.0–18.0)
ICU stay (h)	20 (19–26)	21 (20–44)	25 (20–46)[a]
Hospital stay (d)	8 (6–12)	8 (7–15)	11 (9–16)[a]

Data are expressed as number (percent), median (interquartile range), or mean ± SD. DM, Diabetes mellitus; IABP, intraaortic balloon pump; DSWI, deep sternal wound infection; UTI, urinary tract infection; RBC, red blood cell; FFP, fresh frozen plasma.

[a] $P < 0.05$ non-DM *vs.* DM HbA_{1c} >6.5%.

[b] $P < 0.05$ DM HbA_{1c} <6.5% *vs.* DM HbA_{1c} >6.5%.

[c] $P < 0.05$ non-DM *vs.* DM HbA_{1c} <6.5%.

cemic control before surgery reduces complications as seen in the medical patient population (19).

The impairment of tissue insulin sensitivity is the primary cause of perioperative hyperglycemia and the "diabetes of the injury" (3, 4). Due to the specific metabolic and endocrine alterations induced by extracorporeal circulation, insulin sensitivity not surprisingly decreased during CPB in all patients, with poorly controlled diabetic patients showing the greatest decline. Although hyperglycemia has been shown to be an independent risk factor for death, cardiovascular, respiratory, infectious, and renal complications in nondiabetic and diabetic surgical patients (6–9), the clinical significance of altered insulin sensitivity is unknown. Furthermore, it is still controversial whether the diagnosis of diabetes mellitus *per se* or the actual degree of insulin dysfunction and hyperglycemia contributes to mortality and morbidity in patients undergoing cardiac surgery (20–25). This controversy is illustrated by the fact that only eight of 19 preoperative risk assessment scores include diabetes mellitus (26).

TABLE 4. OR of outcomes for every decrease in insulin sensitivity by 1 $mg \cdot kg^{-1} \cdot min^{-1}$

Outcome	OR (95% CI)	*P* value
Major complications	2.23 (1.30–3.85)	0.004
Death	2.33 (0.94–5.78)	0.067
IABP	1.55 (0.66–3.66)	0.318
Dialysis	1.79 (0.52–6.18)	0.359
Stroke	2.60 (0.64–10.5)	0.181
Severe infection	4.98 (1.48–16.8)	0.010
Minor infection	1.97 (1.27–3.06)	0.003

The ORs were adjusted for potential confounders. CI, Confidence interval; IABP, intraaortic balloon pump.

Studies in nondiabetic patients undergoing open cholecystectomy show a 50% reduction of postoperative insulin sensitivity with unclear impact on outcome (27). The present study demonstrates, to our knowledge for the first time, a significant association between the magnitude of insulin resistance during cardiac surgery and outcome, independent of the patient's diabetic state. This finding lends further support to the previously held contention that, perioperatively, alterations in glucose homeostasis are better predictors of adverse events

than the presence of diagnosed or suspected diabetes mellitus (28, 29).

We acknowledge several limitations of our study. Because perioperative administration of dextrose has been shown to reduce insulin resistance and improve outcomes after noncardiac surgery (30), applying the hyperinsulinemic-normoglycemic clamp itself might have influenced the incidence of complications. However, all patients enrolled in the present protocol received identical treatment.

Although patients not known for diabetes and presenting with blood glucose levels greater than 7.0 mmol · liter^{-1} or HbA_{1c} greater than 6.0% were not eligible, we cannot entirely exclude the possibility that some patients who were labeled "nondiabetic" actually had diabetes mellitus. This is another limitation of the study.

Because there is no accepted HbA_{1c} value to distinguish between diabetic patients with good and poor glycemic control, using an HbA_{1c} value of 6.5% is, to some extent, arbitrary. The decision to use 6.5% in the present protocol was based on recent recommendations (15).

In conclusion, in diabetic patients preoperative HbA_{1c} levels predict insulin sensitivity during cardiac surgery and, possibly, outcome. Independent of the patient's diabetic state, intraoperative insulin resistance is associated with an increased risk of complications after surgery.

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