Statin Intake Is Associated With Decreased Insulin Sensitivity During Cardiac Surgery

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OBJECTIVE—Surgical trauma impairs intraoperative insulin sensitivity and is associated with postoperative adverse events. Recently, preprocedural statin therapy is recommended for patients with coronary artery disease. However, statin therapy is reported to increase insulin resistance and the risk of new-onset diabetes. Thus, we investigated the association between preoperative statin therapy and intraoperative insulin sensitivity in nondiabetic, dyslipidemic patients undergoing coronary artery bypass grafting.

RESEARCH DESIGN AND METHODS—In this prospective, nonrandomized trial, patients taking lipophilic statins were assigned to the statin group and hypercholesterolemic patients not receiving any statins were allocated to the control group. Insulin sensitivity was assessed by the hyperinsulinemic-normoglycemic clamp technique during surgery. The mean, SD of blood glucose, and the coefficient of variation (CV) after surgery were calculated for each patient. The association between statin use and intraoperative insulin sensitivity was tested by multiple regression analysis.

RESULTS—We studied 120 patients. In both groups, insulin sensitivity gradually decreased during surgery with values being on average ~20% lower in the statin than in the control group. In the statin group, the mean blood glucose in the intensive care unit was higher than in the control group (153 ± 20 vs. 140 ± 20 mg/dL; $P < 0.001$). The oscillation of blood glucose was larger in the statin group (SD, $P < 0.001$; CV, $P = 0.001$). Multiple regression analysis showed that statin use was independently associated with intraoperative insulin sensitivity ($\beta = -0.16$; $P = 0.03$).

CONCLUSIONS—Preoperative use of lipophilic statins is associated with increased insulin resistance during cardiac surgery in nondiabetic, dyslipidemic patients.

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Hypercholesterolemia has long been recognized as a risk factor for atherosclerosis and coronary heart disease. As cholesterol-lowering agents such as hydroxymethylglutaryl CoA reductase inhibitors (statins) reduce cardiovascular morbidity (1), the American College of Cardiology/American Heart Association (ACC/AHA) recommends their use in patients with unstable angina or myocardial infarction (2). Further evidence suggests that patients undergoing surgical and nonsurgical coronary revascularization procedures can benefit from the anti-inflammatory properties of statins (3,4). Accumulated results showing a reduced incidence of ischemic events and arrhythmias in the presence of statin therapy (5,6) prompted the ACC/AHA to advocate for the administration of statins in coronary artery bypass grafting (CABG) (7) and in noncardiac surgery (8).

More recent studies indicate that statins increase the risk of new-onset diabetes (9–12). In particular, the use of atorvastatin has been shown to cause insulin resistance in hypercholesterolemic, nondiabetic patients (13). This metabolic effect of statin therapy is relevant for patients undergoing major surgery, who typically, as a result of stress-induced endocrine changes, develop hyperglycemia and insulin resistance, the so-called diabetes of the injury (14,15). On the basis of previous observations demonstrating a significant relationship between intraoperative insulin sensitivity and major complications after cardiac surgery (16,17), we investigated whether statin therapy is associated with decreased insulin sensitivity in nondiabetic, dyslipidemic patients undergoing CABG.

RESEARCH DESIGN AND METHODS

Patients and surgery

This study was conducted according to the Declaration of Helsinki. With approval from the McGill University Health Center Research Ethics Board, we included patients scheduled for elective CABG at the Royal Victoria Hospital (between October 2008 and March 2010) in this comparative, prospective, nonrandomized study. Patients were screened for inclusion and exclusion criteria and statin use. After obtaining written informed consent, patients taking lipophilic statins (atorvastatin or rosuvastatin) for at least 3 months were assigned to the statin group, whereas consenting, hypercholesterolemic patients not receiving any statins (LDL cholesterol >100 mg/dL) were allocated to the control group.

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 ≥0.5 ng/L. Patients with a confirmed diagnosis of type 2 diabetes and receiving treatment (oral antihyperglycemic agents or insulin) were also excluded. Patients not known to have diabetes presenting with blood glucose levels >7.0 mmol/L (126 mg/dL) or glycated hemoglobin A_{1c} (HbA_{1c}) >6.0% were also not eligible.

Patients received standardized general anesthesia using sufentanil and midazolam supplemented with inhaled sevoflurane.

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During cardiopulmonary bypass (CPB), mean arterial pressure was maintained between 50 and 70 mmHg. Moderate hemodilution (hematocrit 20–25%) and mild hypothermia (34°C) were tolerated during CPB.

Measurements

Insulin sensitivity was assessed by the hyperinsulinemic-normoglycemic clamp technique, the gold standard to quantify insulin sensitivity in humans. Before induction of anesthesia, insulin (Humulin R; Eli Lilly and Company, Indianapolis, IN) was intravenously administered at 5 $mU \cdot kg^{-1} \cdot min^{-1}$. Approximately 10 min after starting the insulin infusion, and when the blood glucose was <6.1 mmol/L (110 mg/dL), 20% dextrose supplemented with phosphate (30 mmol/L) 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/L (90 mg/dL). The dextrose infusion rate during steady-state conditions, before, during, and toward the end of CPB, was used as an indicator of insulin sensitivity. We assumed steady-state conditions if the coefficient of variation (CV) of five subsequent dextrose infusion rates was <5%. Percentage changes in insulin sensitivity between baseline (after anesthesia induction before surgery) and the end of CPB were calculated in each group.

At the end of surgery (skin closure), the insulin infusion was stopped. The dextrose infusion was maintained for 2 h to avoid hypoglycemia. If the blood glucose was >8.0 mmol/L (144 mg/dL), an insulin infusion of 2 units/h was started in the intensive care unit (ICU). This was then titrated according to the following insulin sliding scale, aiming at a blood glucose between 4.0 and 8.0 mmol/L (72 and 144 mg/dL): if blood glucose >10.0 mmol/L (180 mg/dL), increase insulin infusion by 3 units/h; 8.0–10.0 mmol/L (144–180 mg/dL), increase insulin infusion by 2 units/h; 6.1–7.9 mmol/L (109–143 mg/dL), increase insulin infusion by 1 unit/h; 4.0–6.0 mmol/L (72–108 mg/dL), maintain current insulin infusion rate; <4.0 mmol/L (71 mg/dL), stop insulin infusion and administer 10 mL of 20% dextrose; or drops to a lower blood glucose range, maintain current insulin infusion rate.

Blood glucose was measured hourly, and the average blood glucose during the first 24 h after surgery was calculated. In each patient, the mean and SD of blood glucose concentration after surgery were calculated as arithmetical mean and SD of the entire set of measurements postoperatively. To evaluate relative variability, the CV (SD/average blood glucose) was also calculated for each patient (18).

Statistics

A previous study reported that insulin sensitivity decreased toward the end of CPB during cardiac surgery (16). In the present study, the primary outcome was lowest insulin sensitivity, i.e., insulin sensitivity at the end of CPB. The secondary outcome was blood glucose control in the ICU. Data are presented as means ± SD or number (percentage). Patient demographics were compared using Student *t* test or χ^2 test for categorical variables. Insulin sensitivities at each time point, percentage changes of insulin sensitivity, mean blood glucose values, and SD and CV of blood glucose between the two groups were compared using Student *t* test. Insulin sensitivity was compared using two-way ANOVA with repeated measures across time and a comparison across groups. Multiple regression analysis was performed to determine factors related to intraoperative insulin sensitivity at the end of CPB. The variables used for the analysis were age, BMI, HbA_{1c}, fasting blood glucose, homeostatic model assessment of insulin resistance (HOMA-IR), total cholesterol, HDL cholesterol, triglycerides, LDL cholesterol, systolic blood pressure, use of ACE inhibitors, use of β-blockers, use of Ca-channel blockers, use of statins, and baseline level of insulin sensitivity. Two-sided *P* values <0.05 were considered statistically significant.

The sample size was calculated based on the result of a previous investigation showing ~10% increased insulin resistance (HOMA-IR) by statin therapy (13). In order to achieve a power level of 90%, with an α error of 5%, 60 patients were required in each group. All statistical analyses were performed using SPSS 19 for Windows (IBM, Chicago, IL) and PASS 11 (NCSS, Kaysville, UT).

RESULTS—We enrolled 123 nondiabetic, dyslipidemic patients, 62 of whom were taking statins and 61 who were not taking statins. Once the statin group had 62 patients, we stopped assessing patients

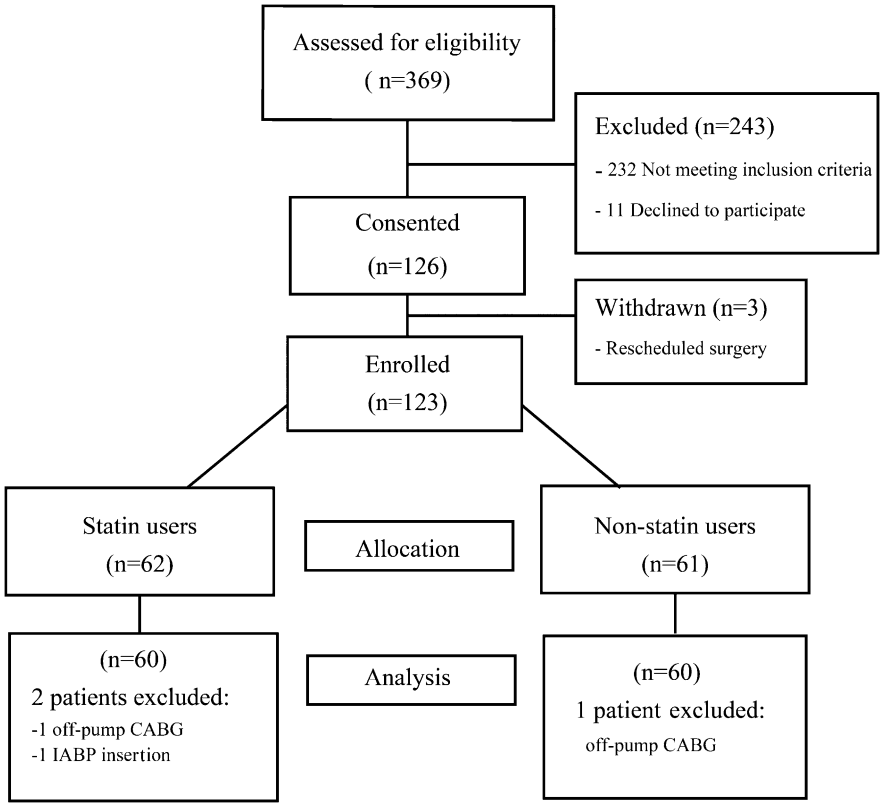

Figure 1—*Patient distribution. Patients* (n = *369) were assessed for eligibility, and 123 patients were enrolled. After allocation, three patients were excluded, one for intra-aortic balloon pump (IABP) insertion before CPB and two for switched surgical procedure to off-pump CABG.*

on statins for the study and then only approached hypercholesterolemic patients not on statins. After allocation, three patients were excluded, two for switched surgical procedures to off-pump CABG and one for requirement for intra-aortic balloon pump during surgery (Fig. 1).

Patient demographics were similar between groups except for total and LDL cholesterol, which were lower in the statin group (Table 1). Target glycemia was achieved in both groups during surgery (mean blood glucose, 5.1 ± 0.3 mmol/L [92 ± 5 mg/dL] in the statin group and 5.0 ± 0.4 mmol/L [90 ± 7 mg/dL] in the control group; $P = 0.263$). The oscillation of blood glucose during surgery was also comparable (CV, 13.9 ± 3.4% in statin group and 13.7 ± 3.6% in control group; $P = 0.765$).

There was no significant difference of the insulin sensitivity at the baseline point ($P = 0.18$) (Table 2). In both groups, insulin sensitivity gradually decreased toward the end of CPB ($P < 0.001$). The insulin sensitivities were lower in the statin group than in the control group ($P = 0.011$), and the values were on average ~20% lower in the statin than in the control group (Table 2). The magnitude of the change of intraoperative insulin sensitivity was also greater in the statin group compared with the control group (41 ± 17 vs. 27 ± 19%; $P < 0.001$).

In the statin group, the mean blood glucose in the ICU was higher than in the control group (8.5 ± 1.1 mmol/L [153 ± 20 mg/dL] vs. 7.8 ± 1.1 mmol/L [140 ± 20 mg/dL]; $P < 0.001$) (Table 2). The oscillation of blood glucose after surgery was larger in the statin group when compared with the control group (SD, $P < 0.001$; CV, $P = 0.001$) (Table 2). Multiple regression analysis showed that BMI, HDL cholesterol, triglycerides, baseline level of insulin sensitivity, and statin use were independently associated with the insulin sensitivity at the end of CPB (Table 3).

CONCLUSIONS—The results of this prospective, nonrandomized study demonstrate increased insulin resistance during CABG in patients on statin therapy.

Statins are usually given to decrease plasma LDL concentrations and reduce the risk of ischemic heart disease and stroke (1,19). Although the clinical benefits of statins in nonsurgical patients have long been recognized, some evidence also supports their preemptive use in patients undergoing major surgery and cardiac surgery (20–24).

More recently, however, concerns have been raised about potential diabetogenic effects of statins, with potential relevance for surgical patients. Two meta-analyses including >100,000 participants concluded that long-term statin intake increases the risk of new-onset diabetes (9,25). In the JUPITER study (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), which enrolled 17,802 nondiabetic adults, rosuvastatin intake >1.9 years increased the incidence of diabetes by ~20% (26).

Several mechanisms may be responsible for these diabetogenic effects (27). Statins, particularly the lipophilic compounds, have been shown to inhibit glucose-induced cytosolic Ca^{2+} elevations and insulin secretion due to blockade of L-type Ca^{2+} channels in rat islet β-cells (28). In type 2 diabetic mice and human subjects treated for 3 months, atorvastatin impaired glucose tolerance and GLUT4 expression by inhibiting isoprenoid biosynthesis (29). High doses of lipophilic statins decreased insulin secretion from MIN6 β-cell lines, mediated either by the inhibition of hydroxymethylglutaryl CoA reductase or direct cytotoxicity (30). In hypercholesterolemic patients, atorvastatin therapy aggravated insulin resistance and elevated HbA_{1c} levels, which may be the result of decreased plasma adiponectin concentrations (13). On the other hand, major surgical tissue trauma leads to stereotypical alterations in glucose metabolism, including stimulated glucose production and impaired glucose utilization. Much of this metabolic derangement can be explained by specific neuroendocrine changes, such as increased circulating concentrations of cortisol, glucagon, and catecholamines (14). These hormones affect glucose homeostasis by inhibiting insulin secretion and/or counteracting its peripheral action, causing impairment of tissue insulin sensitivity, the so-called diabetes of the injury (15,31). A previous study showed that intraoperative insulin sensitivity decreased toward the end of CPB in cardiac surgery (16). In the present study, preoperative lipophilic statin use together with surgical stress could work synergistically to worse intraoperative insulin sensitivity.

Insulin resistance is a typical feature of the endocrine response to surgery, leading to impaired glucose tolerance and hyperglycemia (15,31). Hyperglycemia has been shown to be an independent risk factor for death and cardiovascular, respiratory, infectious, and renal complications in nondiabetic and diabetic surgical patients (32–34). A link between the impairment of intraoperative insulin sensitivity and

Table 1—*Patient demographics*

	Control	Statin	*P* value
Number (*n*)	60	60	
Age (years)	65 ± 12	64 ± 11	0.74
Weight (kg)	81 ± 17	83 ± 15	0.42
Height (m)	1.69 ± 0.10	1.72 ± 0.08	0.10
BMI (kg/m^2)	28.2 ± 5.3	28.0 ± 4.1	0.80
Sex (male/female)	38 / 22	42 / 18	0.44
HbA_{1c} (%)	5.4 ± 0.5	5.5 ± 0.4	0.23
Fasting blood glucose (mmol/L)	5.7 ± 0.6	5.9 ± 0.9	0.11
HOMA-IR	2.4 ± 1.4	2.6 ± 1.5	0.59
Total cholesterol (mg/dL)	193 ± 40	149 ± 44*	<0.01
HDL cholesterol (mg/dL)	34 ± 11	35 ± 12	0.77
Triglycerides (mg/dL)	138 ± 68	139 ± 68	0.97
LDL cholesterol (mg/dL)	131 ± 32	88 ± 35*	<0.01
Systolic blood pressure (mmHg)	129 ± 23	134 ± 23	0.47
Creatinine (μmol/L)	94 ± 18	92 ± 19	0.43
ACE inhibitors, *n* (%)	26 (43)	32 (53)	0.27
β-Blockers, *n* (%)	42 (70)	38 (63)	0.44
Ca-channel blockers, *n* (%)	8 (13)	7 (12)	0.78
Aortic cross-clamp time (min)	81 ± 27	83 ± 24	0.70
CPB time (min)	100 ± 32	106 ± 34	0.29
Duration of surgery (min)	209 ± 52	216 ± 51	0.49
Lowest T (°C)	33.8 ± 1.1	33.9 ± 1.0	0.68

Data are mean ± SD or number (%). Creatinine, preoperative creatinine plasma concentration; T, core body temperature. *$P < 0.05$ vs. control.

Table 2—*Outcomes*

	Control	Statin
Number (*n*)	60	60
Insulin sensitivity (mg/kg/min)		
Baseline	5.2 ± 1.8	4.9 ± 1.8
Pre-CPB	4.9 ± 1.7	4.1 ± 1.5*
Early CPB	4.1 ± 1.6	3.4 ± 1.4*
Late CPB	3.7 ± 1.5	2.9 ± 1.3*
Blood glucose in ICU (mmol/L)	7.8 ± 1.1	8.5 ± 1.1*
SD of blood glucose (mmol/L)	1.7 ± 0.6	2.2 ± 0.7*
CV of blood glucose (%)	22.1 ± 6.7	26.3 ± 7.3*

Data are mean ± SD. Baseline, after anesthesia induction; early CPB, 15 min after the initiation of CPB; late CPB, 15 min before separation from CPB; pre-CPB, immediately before CPB. *$P < 0.05$ vs. control.

clinical outcomes was observed after elective cardiac surgery, indicating that insulin resistance during surgery, rather than the presence of diabetes per se, is a predictor of major complications, in particular infections (16). Independent of the patient's diabetic state, a reduction of insulin sensitivity by 50% was associated with a five- to sixfold increased incidence of major complications, including 30-day mortality, myocardial failure, stroke, renal failure requiring dialysis, and serious infections (severe sepsis, pneumonia requiring endotracheal intubation, and deep sternal wound infection) (17). Our present finding demonstrating decreased intraoperative insulin sensitivity in the presence of statin therapy may therefore be relevant in the cardiac surgery patient population.

Table 3—*Multiple regression analysis to determine factors related to the insulin sensitivity at the end of CPB*

Independent variable	β	*P* value
Age	−0.01	0.93
BMI	−0.18	0.03
HbA_{1c}	−0.08	0.37
Fasting blood glucose	−0.08	0.31
HOMA-IR	−0.15	0.15
Total cholesterol	0.03	0.76
HDL cholesterol	0.17	0.03
Triglycerides	−0.27	0.01
LDL cholesterol	−0.05	0.49
Systolic blood pressure	0.03	0.78
ACE inhibitors (yes = 1, no = 0)	−0.06	0.56
β-Blockers (yes = 1, no = 0)	−0.10	0.18
Ca-channel blockers (yes = 1, no = 0)	0.06	0.62
Statins (yes = 1, no = 0)	−0.16	0.03
Baseline of insulin sensitivity	0.47	<0.01

Increased insulin resistance by statin intake in the current study worsened glycemic control and resulted in a greater oscillation of blood glucose. There is evidence suggesting that the variability of blood glucose, rather than the absolute glycemic value, influences outcome (18). It has been proposed that fluctuations in glycemia trigger oxidative stress to a greater degree than sustained hyperglycemia (35). Data obtained in critical care showed that ICU survivors experienced less blood glucose variability than nonsurvivors (CV of glucose in survivors, 20 ± 12%; in nonsurvivors, 26 ± 13%) (18). In our study, the CV of postoperative blood glucose in the statin group was greater than in the control group and similar to the value observed in the previously reported nonsurvivor group of critically ill patients.

Supported by some evidence suggesting improved outcomes after cardiac surgery with statin intake (36), current guidelines of the European Society of Cardiology, the ACC, and the AHA recommend their use in patients undergoing CABG (7). These recommendations, however, are based on the results of small, randomized, controlled trials and observational studies and, thus, are inevitably subjected to the influence of potential confounders. The "healthy user effect" with statins has been associated with a reduction in adverse events. These patients who adhere to a medication schedule also engage in a healthy lifestyle and meet a primary care physician more often, which may secondarily result in better outcomes (37). It also must be emphasized that even if cardiovascular end points, i.e., atrial fibrillation and myocardial infarction, are reduced after cardiac surgery, poor glycemic control may have a negative impact on other relatively common, major, noncardiovascular complications, such as infections and renal morbidity. A large, prospective, randomized, controlled trial is needed to determine the clinical relevance of preoperative statin therapy in the cardiac surgery patient population for cardiac and noncardiac events.

We acknowledge several limitations of the study. Depending on their solubility, statins can be categorized as hydrophilic (pravastatin) or lipophilic (atorvastatin and rosuvastatin) (38). Whereas lipophilic statins, particularly when administered in high doses, have pleiotropic effects, such as impairment of insulin secretion and exacerbation of insulin resistance (28,39), hydrophilic statins lower plasma cholesterol to a lesser extent and may in fact reduce the frequency of diabetes, as shown for pravastatin in the West of Scotland Coronary Prevention Study (40). In the present protocol, only patients on lipophilic statins were eligible; therefore, our findings do not apply to patients taking hydrophilic compounds. The current study, although prospective, is not a randomized, double-blinded clinical trial nor is it designed or powered to assess patient outcomes. In conclusion, preoperative use of lipophilic statins is associated with increased insulin resistance during cardiac surgery in nondiabetic, dyslipidemic patients.

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H.S. contributed to statistical analysis and data interpretation and drafted the manuscript. G.C. and R.L. researched data and contributed to discussion. T.Sa., R.H., and T.C.-M. contributed to data collection. T.M. contributed to statistical analysis. T.Sc. reviewed and edited the manuscript. T.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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