Poor Preoperative Left Ventricular Function is Associated With Decreased Insulin Sensitivity During Cardiac Surgery

Takumi Codère-Maruyama, MD,* Hiroaki Sato, MD, PhD,‡ Tamaki Sato, MD,§ Roupen Hatzakorzian, MD, MSc,* Dominique Shum-Tim, MD, MSc,† and Thomas Schricker, MD, PhD*

Objective: **To investigate the association between preoperative left ventricular ejection function (LVEF) and whole-body insulin sensitivity during cardiac surgery.**

Design: **A prospective, non-randomized trial.**

Setting: **A tertiary care hospital setting.**

Participants: **Patients undergoing elective cardiac surgery.**

Interventions: **Consenting, non-diabetic patients scheduled for elective cardiac surgery requiring cardiopulmonary bypass (CPB) were assigned either to a group with normal LVEF (EF $\geq$55%) or one with low LVEF (EF $\leq$45%) as assessed by coronary angiography. Insulin sensitivity was assessed by the hyperinsulinemic-normoglycemic clamp technique before and towards the end of CPB. The association between LVEF and insulin sensitivity was tested using Student t-test.**

Results: **One hundred forty patients were studied, with 48 patients in the low and 92 patients in the normal LVEF group. Patient demographics were similar in both groups except for preoperative LVEF ($p < 0.001$). Before CPB, patients with normal LVEF showed higher insulin sensitivity when compared to patients with low LVEF ($p = 0.04$). Insulin sensitivity decreased towards the end of CPB ($p < 0.001$) in both groups, resulting in similar values.**

Conclusions: **Poor preoperative left ventricular function is associated with reduced insulin sensitivity before the onset of CPB in cardiac surgery.**

KEY WORDS: insulin, glucose, ejection fraction, cardiac surgery, insulin sensitivity

DIABETES LONG HAS BEEN recognized as a predictor of myocardial dysfunction and heart failure, the so-called diabetic cardiomyopathy.[1,2] There is some evidence to suggest that decreased insulin sensitivity, rather than the diagnosis of diabetes per se, is important.[3,4] While this appears to be associated with poor myocardial performance in medical patients,[5–7] the relationship between the 2 variables in patients undergoing surgery is unknown. Taking into account recent reports demonstrating a significant impact of decreased insulin sensitivity on outcomes after cardiac surgery, a better understanding of the link between perioperative insulin sensitivity and cardiac function becomes clinically relevant in this patient population.[8]

The purpose of this study was to test the hypothesis that left ventricular dysfunction before cardiac surgery is associated with impaired intraoperative insulin sensitivity.

METHODS

With the approval of the local research ethics board, written informed consent was obtained from patients scheduled for elective cardiac surgery requiring cardiopulmonary bypass (CPB). Patients scheduled for off-pump or emergency procedures were not eligible. Also excluded were those with troponin I levels $\geq$ 0.5ng/L, left ventricular ejection fraction (LVEF) of 45% to 55%, and type-2 diabetes mellitus. Patients not known to have diabetes presenting with blood glucose levels $>$7.0 mmol/L (126 mg/dL) or glycated hemoglobin A1c (HbA1c) $>$6.0% also were ineligible.

Consenting patients were allocated either to a group with normal LVEF (EF $\geq$55%) or one with low LVEF (EF $\leq$45%) as assessed by preoperative coronary angiography and ventriculography. The rationale for excluding patients with LVEF between 45% and 55% was to generate 2 discrete study groups.

Patients received standardized general anesthesia using sufentanil and midazolam supplemented with inhaled sevoflurane. During CPB, mean arterial pressure was maintained between 50 and 70 mmHg. Moderate hemodilution (hematocrit 20-25%) and mild hypothermia (34°C) were tolerated. Multidose, hypothermic (4°C), hyperkalemic blood cardioplegia (20 mEq/L K^+), supplemented with adenosine and magnesium sulfate, was infused to maintain cardioplegic arrest.

Insulin sensitivity was assessed by the hyperinsulinemic-normoglycemic clamp technique. Before induction of anesthesia, insulin (Humulin R; Eli Lilly and Company, Indianapolis, IN) was intravenously administered at 5 $mU/kg^1/min^1$. Approximately 10 minutes 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) were administered. Arterial blood glucose concentrations were determined every 5 minutes, and the dextrose infusion was adjusted to maintain blood glucose at 5 mmol/L (90 mg/dL). The dextrose infusion rate in mg/kg/min during steady-state conditions, before and towards the end of CPB, was used as an indicator of insulin sensitivity. The authors assumed steady-state conditions if the coefficient of variation of 5 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.

Continuous variables were expressed as mean $\pm$ SD and categoric variables as numbers with percentages. Patient demographics were compared using Student t-test or χ^2 test for categoric variables. Insulin sensitivities at each time point and mean blood glucose values between the 2 groups were compared using Student t-test. Insulin sensitivity was compared using 2-way ANOVA with repeated measures across time

*From the Departments of *Anesthesia and †Cardiac Surgery, McGill University, Montreal QC, Canada, and the Departments of ‡Anesthesiology, and §Endocrinology, Yamanashi University, Yamanashi, Japan.*

Address reprint requests to Takumi Codère-Maruyama, MD, Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Room C5.20, Montreal, Quebec, Canada H3A 1A1. E-mail: takumi.coderemaruyama@mail.mcgill.ca

1053-0770/2601-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2013.12.017

and groups. All tests were 2-sided, and $p < 0.05$ was considered to be statistically significant.

The sample size was calculated based on a previous investigation showing a 55% decrease in insulin sensitivity (HOMA-IR) in patients with LVEF <40%.[6] In order to achieve a power level of 90%, with an α error of 5%, 47 patients were required in each group.

All statistical analyses were performed using JMP statistical software (version 8, SAS Institute Inc., Cary, NC).

RESULTS

The authors studied 140 patients with 48 patients in the low and 92 patients in the normal LVEF groups. Patient demographics were similar in both groups except for preoperative LVEF ($p < 0.001$) (Table 1).

Target glycemia was achieved in both groups during surgery ($p = 0.52$) (Table 2). Before CPB, patients with poor LVEF showed reduced insulin sensitivity when compared to patients with normal LVEF ($p = 0.04$) (Table 2). It decreased towards the end of CPB ($p < 0.001$) (Table 2) in both groups, resulting in similar values.

DISCUSSION

The results of the present study demonstrated an association between preoperative LVEF and insulin sensitivity before CPB in non-diabetic patients undergoing cardiac surgery. Patients with compromised myocardial function (LVEF ≤ 45%) had a 15% lower insulin sensitivity before the initiation of CPB than patients with normal LVEF (≥55%). Towards the end of CPB, this difference was no longer observed, resulting in similar insulin sensitivities in both groups.

The link between abnormal myocardial function and impaired glucose homeostasis in non-surgical patients has been well recognized. Heart failure has been shown to relate to decreased tissue insulin sensitivity.[3,9,10] Substantial evidence indicates that early diastolic dysfunction is associated with impaired glucose metabolism. For example, Celentano et al demonstrated functional myocardial abnormalities in subjects with diabetes and with impaired glucose tolerance when compared with normoglycemic subjects.[5] Dinh et al reported a prevalence of left ventricular diastolic dysfunction in 92% of subjects with abnormal insulin sensitivities.[11] On the other hand, positron emission tomography (PET) studies in patients with systolic dysfunction (mean LVEF 37%) but without history of diabetes or coronary artery disease demonstrated that abnormal glucose metabolism was associated with more severe LV dysfunction.[6] In the Jackson Heart Study, a longitudinal community-based cohort study, LV mass index, posterior wall thickness and low LVEF were linked with fasting blood glucose levels and decreased insulin sensitivity.[7] Of note, all the above studies have used either the glucose tolerance test or the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) as a measure of insulin sensitivity. In the present study, the authors applied the hyperinsulinemic-normoglycemic clamp technique, the gold standard for measuring insulin sensitivity in humans. Glucose requirement (mg/kg/min) during the clamp was used as a measure of insulin sensitivity (Fig 1).

Although the association between cardiac dysfunction and abnormal insulin sensitivity has been described, the exact underlying pathophysiologic mechanisms are poorly understood. Whether decreased insulin sensitivity is a primary or secondary consequence of heart failure remains uncertain. Nevertheless, ventricular remodeling appears to implicate hyperglycemia and hyperinsulinemia as causative factors. Rats

Table 1. Patient Demographics

	Normal LVEF	Low LVEF	p Value
Number (n)	92	48	
Age (yrs)	67.5 ± 11.7	65.3 ± 11.3	ns
Gender (Male/Female)	66(71.7)/26(28.3)	37(77.1)/11(22.9)	ns
Body mass index (kg/m^2)	26.4 ± 4.1	27.3 ± 4.4	ns
HbA1c (%)	5.4 ± 0.4	5.5 ± 0.4	ns
Fasting blood glucose (mmol/L)	5.7 ± 0.9	5.8 ± 0.8	ns
HOMA-IR	2.6 ± 1.6	2.5 ± 1.5	ns
Ejection fraction (%)	61 ± 4	36 ± 9*	p < 0.001
CABG surgery	45 (48.9)	29 (60.4)	ns
Valve surgery	27 (29.3)	11 (22.9)	ns
CABG + valve surgery	20 (21.7)	8 (16.7)	ns
Mean blood pressure (mmHg)	87.1 ± 18.2	81.5 ± 14.1	ns
Creatinine	98.2 ± 41.2	91.6 ± 21.9	ns
Aortic cross-clamp time (min)	83.4 ± 30.1	86.2 ± 34.2	ns
CPB time (min)	101.7 ± 35.7	117.8 ± 63.6	ns
Surgery time (min)	214.2 ± 63.6	237.9 ± 95.1	ns
Minimum temperature (°C)	32.7 ± 3.2	33.6 ± 1.9	ns
Hypertension	74 (80.4)	42 (87.5)	ns
Coronary artery disease	66 (71.7)	39 (81.3)	ns
Smoking	6 (6.5)	6 (12.5)	ns

NOTE: Data are mean ± SD or number (%).

Abbreviations: CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; creatinine, preoperative creatinine plasma concentration; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; LVEF, left ventricular ejection fraction.

*$p < 0.05$ *v* normal LVEF.