

Perioperative insulin resistance and outcome

Thomas Schricker

Department of Anesthesia, McGill University, Department of Anaesthesia, Royal Victoria Hospital, Montreal, Canada

Terminology

Insulin is the chief anabolic hormone in the human body. It is most recognized for its role in regulating glucose homeostasis by facilitating glucose disposal and suppressing endogenous glucose production. Insulin also plays a pivotal role in promoting fat storage and protein synthesis, and inhibiting lipolysis and protein breakdown. It is less known that insulin exerts non-metabolic effects including vasodilatory, anti-inflammatory, anti-oxidative, anti-fibrinolytic, and positive inotropic effects with potential clinical impact (1,2).

Insulin resistance can be defined as any condition, whereby a normal concentration of insulin produces a subnormal biological response. This umbrella term may comprise states of insulin insensitivity, insulin unresponsiveness, or a combination of both. Although the terms insulin sensitivity and insulin responsiveness are often used interchangeably, their difference stems from the classic sigmoidal dose-response curve of insulin action (3). Insulin sensitivity is characterized by the insulin concentration required to achieve a half-maximal biological response, whereas insulin responsiveness is defined by the maximal effect attained. Impaired insulin sensitivity is, therefore, represented by a rightward shift in the insulin-dose response curve, and decreased responsiveness corresponds to a height reduction of the curve. Proper use of these terms is important because they reflect different defects in insulin action: insulin insensitivity appears to be more implicated in alterations at the pre-receptor and receptor level, whereas decreased responsiveness is related to post-receptor defects (3).

Assessment

The gold standard for the direct assessment of insulin resistance in humans is the hyperinsulinaemic-normoglycaemic clamp technique, whereby insulin is infused at a constant rate to obtain a steady state insulin concentration above the fasting level (4). Based on frequent measurements of plasma glucose levels, glucose is intravenously infused at variable rates to maintain normoglycaemia (4-6 mmol.L⁻¹). Given that endogenous glucose production is completely suppressed, the glucose infusion rate (under steady state conditions) is reflective of glucose disposal, and is, therefore, an indicator of peripheral insulin resistance: the greater the glucose infusion rate the more sensitive the body is to insulin and *vice versa*.

Perioperative insulin resistance

Pathophysiology

Insulin resistance is a central feature of the endocrine response to surgical tissue trauma triggering metabolic changes known as the catabolic response to surgery.

Much of this metabolic-endocrine derangement can be explained by the increased secretion of pituitary hormones and activation of the sympathetic nervous system, resulting in elevated plasma levels of cortisol, glucagon, growth hormone, and catecholamines. These so-called counter-regulatory hormones impair tissue insulin sensitivity, either directly or indirectly, by inhibiting insulin secretion and/or counteracting its peripheral action (5). Furthermore, some evi-

dence demonstrates a relationship between the time course of peri-operative interleukin 6 plasma concentrations and insulin resistance suggesting that inflammatory mediators (cytokines) may also be involved (6).

Although some data indicate reduced glucose uptake in adipose tissue after surgery (7) it is reasonable to assume that the main site for surgery-induced insulin resistance is skeletal muscle, because this is the quantitatively most important organ for insulin-mediated glucose uptake (8).

The magnitude of whole body insulin resistance, which is most pronounced on the day after surgery (up to 70% reduction) and lasts for about three weeks after uncomplicated elective abdominal operations, has been primarily linked to the invasiveness of surgery (9,10).

At present it is not clear if and to what extent other factors contribute including

- duration of trauma (11)
- bed rest and immobilization (12)
- type of anaesthesia and analgesia (13,14)
- nutrition and preoperative fasting (15,16)
- blood loss (9)
- physical status and post-surgery rehabilitation (17)

Outcome

Studies performed over a 6-year period in Sweden (1990-1996, n=60) demonstrate a significant correlation between the degree of the patient's insulin sensitivity on the first postoperative day and length of hospital stay ($r=0.53$, $P=0.0001$) (9). We recently were able to show a significant association between the magnitude of insulin resistance during cardiac surgery and outcome (18). Independent of the patient's diabetic state, for every decrease in intra-operative insulin sensitivity by 20% the risk of a serious complication including all-cause mortality, myocardial failure requiring mechanical support, stroke, need for dialysis and serious infection (severe sepsis, pneumonia requiring mechanical ventilation, deep sternal wound infection) more

than doubled after open heart surgery (18). These findings lent support to the previously held contention that, peri-operatively, alterations in glucose homeostasis are better predictors of adverse events than the presence of diagnosed or suspected diabetes mellitus itself.

The outcome relevance of insulin resistance may also be reflected by the clinical problems associated with its metabolic sequelae, i.e. the catabolic changes in glucose and protein metabolism also known as "diabetes of the injury".

Glucose catabolism after surgery is characterized by an increased rate of hepatic glucose production and impaired glucose utilization resulting in hyperglycaemia (19). In non-diabetic patients undergoing major abdominal procedures we typically observe blood glucose (BG) values >7 mmol.L⁻¹. The worst glycaemia we see during cardiac surgery with levels frequently exceeding the renal threshold of glucose excretion at 10mmol.L⁻¹ (19). Evidence is mounting that hyperglycemia is a predictor of mortality, and that even moderate increases in BG worsen outcome (20,21). Patients with fasting BG levels >7 mmol.L⁻¹ or random BG levels >11.1 mmol.L⁻¹ on general surgical wards showed an 18-fold increased in-hospital mortality, a longer hospital stay and a greater risk of infection (22).

Protein catabolism is characterized by a net loss of functional and structural body protein. Metabolically healthy patients lose between 40 and 80 g of nitrogen after elective abdominal operations, equivalent to 1.2-2.4 Kg wet skeletal muscle (23). In agreement with findings in diabetic subjects reporting a negative correlation between the degree of insulin resistance and whole-body protein balance, we have shown that protein losses after abdominal surgery are 50% greater in insulin resistant than in normal patients (24). More recent studies indicate a linear relationship between insulin sensitivity and protein balance in parenterally fed patients undergoing open heart surgery (25). Erosion of lean tissue delays wound healing, compromises immune function and diminishes muscle strength. The en-

suing muscle weakness prolongs mechanical ventilation, inhibits coughing, and impedes mobilization, thereby complicating convalescence and causing morbidity (26,27).

Treatment

The therapeutic administration of insulin is an obvious choice to overcome peri-operative insulin resistance and to improve outcome. Provided insulin is given in sufficient amounts, insulin resistance can be normalized in surgical patients (28). Normoglycaemia and whole body protein stores could be preserved by insulin therapy suggesting that insulin sensitivity rather than insulin responsiveness is reduced during and after surgery. Surprisingly to date most studies investigating the impact of insulin therapy on clinical outcomes were not able to normalize insulin sensitivity, and establish normoglycaemia (29-31). Only the Leuven trial demonstrating a large survival benefit for mostly non-diabetic, surgical critical care patients randomized to intensive insulin therapy, was able to strictly maintain a normal BG level (4.4-6.1 mmol.L⁻¹) throughout the study period (32).

Elective surgery is routinely performed after overnight fasting to minimize the risk of aspiration when general anaesthesia is induced. Fasting periods before abdominal surgery sometimes amount to up to 40 hours because obligatory bowel preparation on the preoperative day impedes oral food intake. Animal studies show that coping with stress is much improved if animals enter the trauma fed rather than fasting emphasizing the fact that the avoidance of fasting before surgery could make patients also less vulnerable to complications (33). Overnight treatment with intravenous glucose has been shown to prevent the decrease in muscle insulin sensitivity (15,16), and the early protein loss after gastrointestinal surgery prompting better voluntary muscle function (34). While studies conducted in relatively small patient populations suggested better outcomes with preop-

erative nutrition (35,36), the results of a larger RCT failed to show any clinical benefit (37).

Ample evidence has accumulated to identify the peripheral and central nervous system as a common pathway triggering the catabolic responses to tissue trauma. Blockade of these pathways by epidural local anaesthetics prevents the increase in circulating counter-regulatory hormones, thereby improving insulin sensitivity and limiting catabolism, i.e. protein loss and hyperglycaemia (14,38). These physiological effects of epidural anaesthesia may serve as a rationale for improved respiratory and cardiovascular outcomes after general, urological and vascular procedures as reported by meta-analyses and randomized controlled trials (39,40). Other studies, however, failed to show such benefits, especially when performed in the context of fast track or enhanced recovery after surgery programmes (41).

Predicting insulin resistance and outcome

Plasma glycosylated hemoglobin A (HbA_{1c}) is an indicator of BG control during the previous three to four months. While HbA_{1c} values have been widely investigated as an index of long-term BG control and outcome predictors in diabetic patients, its predictive value in surgical patients has received little attention. Observations made in 273 diabetic and non-diabetic patients undergoing open heart surgery demonstrate a significant correlation between the quality of preoperative glycaemic control as reflected by HbA_{1c} levels and insulin sensitivity during cardiac surgery ($r=0.527$, $P<0.001$) (18). In addition, diabetic patients with a HbA_{1c} >6.5% 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 ICU ($P=0.030$) and the hospital ($P<0.001$) than metabolically normal patients (18). These findings are in agreement with the results of other observational studies indi-

cating worse outcomes after cardiac, abdominal and vascular procedures in the presence of increased HbA1c values (42-44).

If it holds true that poor peroperative glycaemic control adversely affects outcome of diabetic patients, it remains to be studied whether the timely improvement of glycaemic control before surgery by dietary and pharmacological interventions or exercise reduces complications as seen in the medical patient population (45).

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Disclosure

My research is presently funded by the Canadian Institutes of Health Research, the Heart and Stroke Foundation Canada and the Research Institute of McGill University.

In the last two years I have been receiving honoraria for lectures and organizing activities from Baxter Healthcare[®], Deerfield, IL.