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Determination of insulin resistance in surgery: The choice of method is crucial☆

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SUMMARY

Background & aims: In elective surgery, postoperative hyperglycaemia and insulin resistance are independent risk factors for complications. Since the simpler HOMA method has been used as an alternative to the hyperinsulinemic normoglycemic clamp in studies of surgery induced insulin resistance, we compared the two methods in patients undergoing elective surgery.

Methods: Data from 113 non-diabetic patients undergoing elective surgery were used. Insulin sensitivity, both before and after surgery, was quantified by the clamp and HOMA. Pre- and postoperatively, the results of the clamp were compared to HOMA using regression- and correlation analysis. Degree of agreement between the methods was studied using weighted linear kappa and the Bland–Altman test.

Results: Both the clamp and HOMA recorded a mean relative reduction in insulin sensitivity of 39 ± 24% and 39 ± 61% respectively after surgery; with significant correlations ($p < 0.01$) for pre- and post-operative measures as well as for relative changes. However r^2 values were low: 0.04, 0.07 and 0.03 respectively. The degree of agreement for the relative change in insulin sensitivity using the Bland–Altman test gave a mean of difference 0% but "limits of agreement" (±2SD) was ±125%. This poor inter-method agreement was consolidated by a weighted linear kappa value of 0.18.

Conclusion: While the hyperinsulinemic euglycemic clamp measures the postoperative changes in insulin sensitivity, HOMA measures something different. Data using the HOMA method must therefore be interpreted cautiously and is not interchangeable with data obtained from the clamp.

1. Introduction

Hyperglycaemia and insulin resistance have been recognized as a cause for complications in cardiac surgery,[1] in surgical ICU[2,3] and also in major abdominal surgery.[4] One major underlying cause for hyperglycaemia is insulin resistance.[5] Insulin resistance affects all major parts of body metabolism,[6] and is usually clinically defined as the inability of a known quantity of insulin (exo- or endogenous) to control glucose levels in an individual as compared to the normal control.[7] Insulin achieves glucose control by increasing glucose uptake and utilization primarily in muscle and fat and/or by reducing endogenous glucose production, mainly from the liver (EGP).[8]

Insulin resistance transiently occurs as a fundamental reaction to injury including trauma and surgery but also in response to other types of physical stress such as fasting,[9,10] pain,[11] and immobilization.[12] The magnitude of insulin resistance is related to the degree of injury/stress and it remains altered up to several weeks after medium size elective abdominal surgery.[5] Previous studies have shown a sevenfold variation in M-values (A measure of insulin sensitivity) in the preoperative control state among non-diabetic surgical patients.[5] However, the relative reduction in M-values after a given surgical operation remains relatively constant.[5] In elective surgery, insulin resistance has been closely associated with complications.[1,13] Several readily available perioperative treatments reduce post-operative insulin resistance, including many of the components of the Enhanced Recovery or ERAS programs.[14]

With the growing interest in insulin resistance associated with surgery and stress, an increasing number of investigations have

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been published in this topic. Quite different results have emerged from studies of similar kind.[15,16] However, when reviewing the literature and the contradictions, a likely reason for the discrepancies is the use of different methods to determine insulin sensitivity.

So how should insulin sensitivity be measured? The hyperinsulinemic euglycemic clamp (M-value) is well documented as reference method for direct measurement of whole body insulin sensitivity and therefore considered the "golden standard".[7,17] Most commonly, the clamp method assesses glucose dynamics at physiological hyperinsulinemia (levels seen after meals)[17]. A disadvantage is that the method is labour intensive, expensive and requires some training and experience in order to provide data that are reproducible and reliable. Therefore the cheaper and easier calculated HOMA index (Homeostasis Model Assessment) has often been used as an alternative method to determine insulin resistance.[18] HOMA is calculated using basal fasting glucose and insulin levels when the activity of insulin is minimal which is obviously different from the clamp method. Nevertheless, many authors using HOMA also make conclusions and comparisons with published data achieved using the glucose clamp.[15,17,19,20] The question is: does it really measure the same thing and is it interchangeable with the clamp in surgical patients? We decided to compare HOMA to the clamp method in studies of surgery induced insulin resistance.

2. Materials and methods

Data from 113 non-diabetic patients undergoing elective surgery between the years 1989–2006 were used. These have been published in several previous original reports.[21–31] The term non-diabetic defined as having no history, symptoms or signs of diabetes; no medication for diabetes and a fasting glucose <6 mmol/l. HbA1c was not measured routinely in all patients. The surgical procedures performed included both open and laparoscopic operations and varied from colorectal-, upper GI-, general- and orthopaedic surgery, Table 1. This ensured a wide range of insulin resistance. Sliding scales for insulin treatment were used throughout the studies, but only one patient required intervention with insulin in the perioperative period.

The regional ethical committee approved all original studies, as well as the current post-hoc analysis. In the current comparison, whole body insulin sensitivity, both before and after surgery, was quantified by the clamp method and compared with the values attained by the calculation of HOMA. This enabled comparisons both at the basal, un-stressed, control situation as well as in the postoperative state, and additionally the calculation of relative change in insulin resistance using the two different methods.

In order to maintain euglycemia during the clamp, infusion of glucose was adjusted manually in 84 of the patients and computer controlled using "Artificial Pancreas" (Biostator®, Life Science Instruments, Miles Laboratories, Elkhart, Indiana, USA) in the remaining 29 patients.

All measurements were performed at similar time intervals. Blood glucose concentrations were determined instantly upon collection by use of the glucose oxidase method[32] (Yellow Springs Instruments Co., Ohio, USA/Biostator®) and serum insulin concentrations were measured using radioimmunoassay (RIA).[33] All measurements were performed at similar time intervals and the same research group conducted the clamp (as described below) using strict protocols in order to gain robust primary data.[17]

2.1. The hyperinsulinemic normoglycemic clamp technique

After fasting overnight, before both the pre- and postoperative clamp, the patient arrives to the laboratory at about 07.30 am. Indwelling peripheral venous catheters are placed. To arterialize venous blood, the sampling arm is placed in a heating sleeve and after 15 min basal glucose and insulin samples are collected.

Insulin is infused intravenously at a constant rate of 0.8 mU/kg/min to yield hyperinsulinemic steady-state at insulin levels seen after a normal meal.[17] The resulting fall in blood glucose level is counteracted by a variable infusion of glucose intravenously to maintain euglycemia within the normal range (4.5–5 mmol/l). After approximately 60 min, plasma insulin, blood glucose and the glucose infusion rate (GIR, mg glucose/min/kg body weight) all reach steady state. With the blood glucose level now constant and with the hyperinsulinemic state, the GIR (now denoted M-value) equals the rate by which insulin disposes glucose from the blood into tissues with insulin dependent glucose uptake, mainly muscle and fat given that EGP is completely suppressed. This could be assumed to be the case in the control situation. In the postoperative, insulin resistant situation, however this might not be entirely true since, due to hepatic insulin resistance, an on going EGP might be present also during hyperinsulinemia in the high physiological range.[22] However, any change in GIR should reflect the combined reduction in insulin effects to stimulate peripheral glucose uptake and to suppress EGP, and therefore gives an estimate of the change in whole-body insulin sensitivity. Consequently, the lower the M-value the greater the resistance to insulin.

HOMA is based on fasting glucose and insulin levels and the index is calculated as follows:

HOMA = Go × Io/22.5, where Go = fasting glucose concentration (mmol/L), Io = fasting plasma insulin concentration μU/ml.[18]

The greater the level of insulin resistance the higher the HOMA value.

2.2. Statistical methods

The results of the clamp were compared to HOMA using regression- and correlation-analysis. The degree of agreement and interchangeability between the methods was studied using weighted linear kappa, K with 4 categories (representing the 25 percentiles in magnitude of insulin resistance)[34,35] and the Bland–Altman test.[36] The latter was used testing the relative changes pre vs. post-operatively using absolute values of the respective methods.

Table 1
Demographic and operative characteristics of patients. None of the patients had any history, signs or symptoms of metabolic disease, nor kidney- or liver disease. Furthermore, they had no medication known to affect intermediary metabolism or gastric emptying. Most had no medication at all and were classified as American Society of Anaesthesiologists (ASA) physical status 1–2.

Patient data		
Sex ratio (M:F)	60:53	
Age (years)[a]	55 ± 13	
BMI (kg/m^2)[a]	25 ± 3	
Weight (kg)[a]	73 ± 12	
Operative procedure		
Elective open colorectal surgery	$n = 50$	Segmental colorectal resections, including abdominoperineal resection, and Hartmann reversal.
Elective total hip replacement	$n = 31$	
Open cholecystectomy	$n = 17$	
Laparoscopic cholecystectomy	$n = 6$	
Open inguinal hernia repair	$n = 6$	Modified Bassini repair
Elective open urological surgery	$n = 3$	Radical prostatectomy/ Nephrectomy

[a] Values are mean ± SD.

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