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Validation of different measures of insulin sensitivity of glucose metabolism in dairy cows using the hyperinsulinemic euglycemic clamp test as the gold standard

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ABSTRACT

The aim of the present research was to compare different measures of insulin sensitivity in dairy cows at the end of the dry period. To do so, 10 clinically healthy dairy cows with a varying body condition score were selected. By performing hyperinsulinemic euglycemic clamp (HEC) tests, we previously demonstrated a negative association between the insulin sensitivity and insulin responsiveness of glucose metabolism and the body condition score of these animals. In the same animals, other measures of insulin sensitivity were determined and the correlation with the HEC test, which is considered as the gold standard, was calculated. Measures derived from the intravenous glucose tolerance test (IVGTT) are based on the disappearance of glucose after an intravenous glucose bolus. Glucose concentrations during the IVGTT were used to calculate the area under the curve of glucose and the clearance rate of glucose. In addition, glucose and insulin data from the IVGTT were fitted in the minimal model to derive the insulin sensitivity parameter, Si. Based on blood samples taken before the start of the IVGTT, basal concentrations of glucose, insulin, NEFA, and β-hydroxybutyrate were determined and used to calculate surrogate indices for insulin sensitivity, such as the homeostasis model of insulin resistance, the quantitative insulin sensitivity check index, the revised quantitative insulin sensitivity check index and the revised quantitative insulin sensitivity check index including β-hydroxybutyrate. Correlation analysis revealed no association between the results obtained by the HEC test and any of the surrogate indices for insulin sensitivity. For the measures derived from the IVGTT, the area under the curve for the first 60 min of the test and the Si derived from the minimal model demonstrated good correlation with the gold standard.

1. Introduction

Insulin resistance is defined as a state where a normal concentration of insulin evokes a less than normal biological reaction [1]. Development of a transient state of insulin resistance at the end of pregnancy and the beginning of lactation is an important homeorhetic adaptation mechanism of mammals to preserve sufficient glucose for the growing fetus and the nursing neonate [2,3]. In dairy cows genetically selected for high-milk production, these homeorhetic adaptation mechanisms are driven to extremes [4]. Insulin resistance in the transition period has been associated with several pathological conditions like ketosis and cystic ovarian disease [5,6]. Several researchers

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have tried to identify risk factors for the development of increased insulin resistance [7,8] or investigated potential modifying effects of nutritional strategies [9–11] or nutritional [12,13] or pharmacological [10,14,15] substances on the degree of peripheral tissue insulin sensitivity in dairy cows. The conclusions are difficult to appraise and compare because these investigations used different and often nonvalidated methods to assess insulin sensitivity in dairy cows.

The gold standard to measure insulin sensitivity is the hyperinsulinemic euglycemic clamp (HEC) test described by Defronzo et al [16]. Under hyperinsulinemic conditions, the concomitantly infused glucose is taken up primarily by insulin sensitive tissues allowing evaluation of peripheral insulin sensitivity and responsiveness. Unfortunately, HEC tests are laborious and expensive, therefore other tests to evaluate insulin sensitivity have been developed. The disappearance of glucose after an intravenous glucose challenge has frequently been used as a more practical way of measuring insulin sensitivity. The area under the curve (AUC) and the clearance rate (CR) are calculated based on the glucose concentration during the intravenous glucose tolerance test (IVGTT) [8,9]. These measures rely on the assumption that the disappearance of glucose will be slower in insulin resistant individuals. Bergman et al [17] described the use of a mathematical model, the minimal model, based on the glucose and insulin dynamics during an IVGTT. Based on the parameters derived from this model, an index of insulin sensitivity (Si) can be calculated. In humans, surrogate indices for insulin sensitivity have been proposed based on the analysis of glucose, insulin, NEFA, and β-hydroxybutyrate (BHB) in a single blood sample after an overnight fast. The surrogate indices most frequently used are the homeostasis model of insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI), and the revised quantitative insulin sensitivity check index (RQUICKI) [18,19]. These indices have been applied as a measure of insulin sensitivity in dairy cows as well [20,21], but their use is, to the best of our knowledge not yet fully validated and hence questionable [5,11,22].

Until now, none of the aforementioned methods to measure insulin sensitivity have been compared with the gold standard method in dairy cows. The aim of the present study was to compare insulin sensitivity in dairy cows at the end of the dry period as measured by the HEC test, the IVGTT or the calculated surrogate indices for insulin sensitivity.

2. Materials and methods

All experimental procedures were approved by the ethical committee of the Faculty of Veterinary Medicine (EC2010/149 - University Ghent, Belgium).

2.1. Study design

Ten clinically healthy, pregnant Holstein Friesian dairy cows (upcoming parity 2 to 5) were selected at the beginning of the dry period based on body condition score (BCS) according to the scale of Edmonson et al [23]. Five animals were considered to have a normal BCS (BCS 2.5 to 3.5) and 5 animals were considered to be over conditioned (BCS 3.75 to 5). The study design is described in detail by De Koster et al [7]. Briefly, cows were followed starting 2 mo before the expected parturition date. In the third week (21 to 17 d) before the expected parturition date, cows were weighed and catheters (Cavafix Certo 338–14G, B. Braun, Instrulife, Oostkamp, Belgium) were placed in both jugular veins. After a resting period of 2 h, an IVGTT was performed. The next day, the animals underwent a HEC test. All infusions were administered through the left jugular catheter, whereas blood samples were taken from the right jugular catheter.

2.2. Surrogate indices for insulin sensitivity

The surrogate indices for insulin sensitivity were calculated using the glucose, insulin, NEFA, and BHB concentration as determined in serum samples taken 15 min before the start of the IVGTT. Calculations were performed as described by De Koster and Opsomer [3]:

$$HOMA-IR = glucose(mM) \times insulin\left(\mu\frac{IU}{mL}\right);$$

$$QUICKI = \frac{1}{\log\left(glucose\left(\frac{mg}{dL}\right)\right) + \log\left(insulin\left(\mu\frac{IU}{mL}\right)\right)};$$

$$RQUICKI = \frac{1}{log(glucose\ (mg/dL)) + log(insulin(\mu IU/mL)) + log(NEFA(mM))};$$

$$RQUICKI_{BHB} = \frac{1}{log(glucose(mg/dL)) + log(insulin\ (\mu IU/mL)) + log(NEFA(mM)) + log(BHB(mM))}.$$