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Assessment of insulin sensitivity by the hyperinsulinemic euglycemic clamp: Comparison with the spectral analysis of photoplethysmography

Aglecio Luiz De Souza *, Gisele Almeida Batista, Sarah Monte Alegre

Department of Internal Medicine, Faculty of Medical Sciences - State University of Campinas (UNICAMP), Campinas, SP, Brazil

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ABSTRACT

Aims: We compare spectral analysis of photoplethysmography (PTG) with insulin resistance measured by the hyperinsulinemic euglycemic clamp (HEC) technique.
Material and Method: A total of 100 nondiabetic subjects, 43 men and 57 women aged 20–63 years, 30 lean, 42 overweight and 28 obese were enrolled in the study. These patients underwent an examination with HEC, and an examination with the PTG spectral analysis and calculation of the PTG Total Power (PTG-TP). Receiver-operating characteristic (ROC) curves were constructed to determine the specificity and sensitivity of PTG-TP in the assessment of insulin resistance.
Results: There is a moderate correlation between insulin sensitivity (M-value) and PTG-TP ($r = -0.64$, $p < 0.0001$). The ROC curves showed that the most relevant cutoff to the whole study group was a PTG-TP > 406.2. This cut-off had a sensitivity = 95.7%, specificity = 84,4% and the area under the ROC curve (AUC) = 0.929 for identifying insulin resistance. All AUC ROC curve analysis were significant ($p < 0.0001$).
Conclusion: The use of the PTG-TP marker measured from the PTG spectral analysis is a useful tool in screening and follow up of IR, especially in large-scale studies.

1. Introduction

The prevalence of diabetes mellitus (DM), which type 2 diabetes mellitus (T2DM) represents 85–95% of cases of diabetes in adults, has increased dramatically to pandemic proportions; its global prevalence was 8.5% of the world population in 2014, 422 million adults, and is predicted to rise 11.6% by 2025. Due to its high prevalence, chronic course, morbidity and mortality, T2DM has become one of the most challenging public health problems in the world. This problem is also reflected in the heavy economic burden placed on the global health care system (Centers for Disease Control and Prevention, 2014).

A higher prevalence of insulin resistance was found in impaired glucose tolerance (IGT) and T2DM subjects. Impaired glucose tolerance is an intermediate stage between normal glucose tolerance and overt diabetes (Lillioja et al., 1993; Reaven, 1988).

Insulin resistance (IR) has long been recognized as a strong predictor of T2DM, because it is a major underlying factor in the T2DM pathogenesis (Lillioja et al., 1993; Reaven, 1988). In addition, IR has been identified as a risk factor for many other diseases, including endothelial dysfunction and cardiovascular disease (DeFronzo & Ferrannini, 1991; Steinberg, Brechtel, Johnson, Fineberg, & Baron, 1994). In fact, most of the complications of T2DM are related to micro and macrovascular issues. This relationship can be explained in part by the effects of IR on the vascular endothelium (Arcaro, 2002; Hsueh & Quiñones, 2003). Beyond the control of glucose homeostasis, insulin exerts control on vascular homeostasis. In the endothelium, insulin simultaneously stimulates the production of the vasodilator nitric oxide (NO) and the vasoconstrictor endothelin-1 (ET-1) through signaling pathways. Insulin resistance has a strong impact on vascular homeostasis, the balance between the production of vasodilator and vasoconstrictor substances shifts that manifests as impaired endothelial function and micro-vessel disease (Hsueh & Quiñones, 2003; Steinberg et al., 1994).

The ability to measure and diagnose insulin resistance is important in order to understand the etiology of T2DM, to examine the epidemiology, and to prevent or delay T2DM and its complications.

Several methods have been employed to assess insulin sensitivity/resistance both in individuals and in study populations. The gold standard for assessing insulin sensitivity is the hyperinsulinemic euglycemic clamp (HEC), which measures the whole body insulin sensitivity in vivo because it directly measures the capacity of insulin to promote glucose utilization under steady-state conditions (DeFronzo, Tobin, & Andres, 1979). However, due to the costs of

Conflicts of Interest: None.

* Corresponding author at: Internal Medicine Department, State University of Campinas (Unicamp), 126 Alexandre Fleming Street, Campinas, SP, 13083970, Brazil. Tel.: +55 19 3521 7155; fax: +55 19 3289 4107.
E-mail addresses: aglecios@fcm.unicamp.br, aglecios@hotmail.com (A.L. De Souza).

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highly trained personnel, and the labor-intensive, time-consuming, and invasive nature of the method, it is not practical or applicable in large-scale epidemiological studies.

For epidemiologic and clinical studies, surrogate measures of insulin resistance have been developed based on mathematical models derived from metabolic blood parameters. These surrogate measures provide a simple estimate for whole body insulin sensitivity with excellent results to predict insulin sensitivity comparable to those of the HEC, and therefore they have been widely used in large scale investigations (Katz et al., 2000; Matsuda & DeFronzo, 1999; Matthews et al., 1985; McAuley et al., 2001). Yet, even though these methods are simpler, less expensive, and less laborious than the HEC method, they are still problematic when applied in a large number of subjects because they require at least one blood sampling, and a laboratory setting for blood analysis and storage. Therefore, the development of new approaches, which are inexpensive, accurate, and non-invasive to evaluate insulin resistance and hence T2DM prevention, have become important in clinical investigations and large-scale studies.

Photoplethysmography (PTG) is an optical measurement technique that can be used to detect blood volume changes in the microvascular bed of tissue (Challoner & Ramsay, 1974). PTG has widespread clinical application as a clinical physiological monitoring, vascular assessment and autonomic function (Allen, 2007; Challoner & Ramsay, 1974). PTG has been intensively investigated in different clinical settings and studies, including heart rate variability analysis (Gil et al., 2010), metabolic syndrome (Chang, Hsiu, Yang, Fang, & Tsai, 2016), endothelial dysfunction (Gopaul et al., 2001; Hayward, Kraidly, Webb, & Collins, 2002) and diabetes (Gandhi & Rao, 2014). A wide variety of algorithms and models derived from PTG analysis have been proposed to study and understand diseases which autonomic nervous system and vascular function could be affected, including diabetes and metabolic disorders (Lewis et al., 2014).

In this study, we compare the spectral analysis of photoplethysmography (PTG) with insulin resistance measured by the hyperinsulinemic euglycemic clamp (HEC) in nondiabetic subjects, comparing the photoplethysmography-total power index (PTG-TP), obtained from spectral analysis, with the M-value of the HEC.

2. Research Design and Methods

2.1. Subjects

The study was approved by the ethics committee of the Faculty of Medical Sciences – State University of Campinas (UNICAMP), and adheres to the ethical principles of the Declaration of Helsinki. All subjects provided written informed consent to participate in the study, including permission to use their data for research purposes. This was a cross-sectional study. A total of 100 subjects, 43 men and 57 women aged 20–63 years, were studied. Participants were recruited by voluntary participation through advertising among the university community. They were invited to attend a health assessment following a minimum fasting period of 8 h. The health assessment included the completion of a detailed medical questionnaire, physical examination, anthropometric measurements, and blood tests. The inclusion criteria were fasting plasma glucose (FPG) <7.0 mmol/L and HbA1c <6.5%, featuring nondiabetic individuals, according to the revised American Diabetes Association criteria (Chamberlain, Rhinehart, Shaefer, & Neuman, 2016); and good general health as determined by physical examination and medical questionnaire. The subjects excluded from the study were individuals: 1) who had major organ disease involving the heart, lung, kidney or the nervous system, and other endocrine diseases; 2) taking drugs known to affect glucose homeostasis; were pregnant; had erratic, accelerated, or mechanically-controlled irregular heart rhythms; 3) wore an automatic external defibrillator device; had arterial fibrillation or flutter; 4) had atrioventricular block; had any implanted electronic device; 5) had dyes recently introduced into the bloodstream, such as methylene blue, indocyanine green, indigo carmine, and fluorescein; 6) had significant levels of dysfunctional hemoglobin, such as carboxyhemoglobin or methemoglobin; 7) had any condition restricting blood flow, such as severe systemic vascular resistance; and/or 8) worn fingernail polish or false fingernails during the testing. Any of these factors could affect the accuracy of peripheral oxygen saturation of arterial hemoglobin (SpO2%) measurement from the pulse oximeter.

2.2. Experimental Procedures and Analytical Methods

Body mass index (BMI) was calculated based on the ratio between body mass (in kg) and squared height (in meters). In all of the study subjects, body composition was evaluated by electrical bioimpedance with a Biodynamics monitor (Biodynamics Corp., Seattle, WA, USA). Arterial blood pressure was measured by aneroid sphygmomanometer. Plasma glucose was measured with the glucose oxidase method using an YSI glucose analyzer (YSI 2300-Stat Plus analyzer; YSI, Yellow Springs, OH, USA). Glycosylated hemoglobin (HbA1c) was measured by high performance liquid chromatography method using a HPLC Variant II (BioRad Inc., Hercules, CA, USA).

2.3. Clamp Study

The hyperinsulinemic euglycemic clamp study, which was carried out after an overnight (12 to 14 h) fast, consisted of 2 h of euglycemic insulin infusion at a rate of 40 mU/min per meter squared of body surface area, and was preceded by a 2-h control period as previously described (DeFronzo et al., 1979). Intracatheters were inserted into an antecubital vein for the infusion of insulin and glucose. A second catheter was inserted retrogradely into a wrist vein, and the hand was placed in a heated box (50–60 °C) for the sampling of arterialized blood. The infusion was adjusted according to glucose determinations made every 5 min on a glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). For calculation of insulin sensitivity, the glucose disposal rate (M-value) (milligrams per kilogram per minute) was calculated from the infusion rate of exogenous glucose during the second hour of the insulin clamp period, M-value was normalized per kg fat-free mass (FFM). M-value <4.8 mg/kg_{ffm}·min was considered as a diagnosis of insulin resistance. This cut off was defined by the lowest quartile of insulin resistance in the background population (Alberti & Zimmet, 1998; Stern et al., 2005; Vistisen, Colagiuri, & Borch-Johnsen, 2009).

2.4. Spectral Analysis of Photoplethysmography

The fingertip oximeter of the ES Complex system device (LD Technology, Miami, Florida, USA) was used to assess photoplethysmography (Adami et al., 2012) (Fig. 1). The fingertip oximeter is a simple and noninvasive optical technique, which is comprised of a pulsatile physiological waveform or photoplethysmography (PTG) attributed to cardiac synchronous changes in the artery blood volume with each heartbeat, and it is used to estimate the skin blood flow using infrared light (Allen, 2007). The oximeter was placed on the right index finger, and it displays in real time the photoelectrical-plethysmography waveform, and the signal processing analysis of the waveform allows to determine PTG-TP by the ES Complex software (Adami et al., 2012; Gandhi & Rao, 2014). The PTG contour analysis has been described in various studies in Asia, Europe, and the United States (Allen, 2007; Chang et al., 2016; Gandhi & Rao, 2014).

In the present study, the PTG contour has been analyzed first using the first derivative (FD), and then analyzed using the fast Fourier transform (FFT) (Fig. 2). The PTG spectral analysis, using Fast Fourier Transforms (FFT) of the total records of the oximeter wave form