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

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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.
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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.

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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

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provides 3 frequencies – high (HF) (From 2.57 to 5 Hz and 2 peaks at 3.2 Hz and 4.58 Hz), low (LF) (from 1.47 to 2.56 Hz and peak at 2 Hz) and very low frequencies (VLF) (from 0 to 1.46 Hz and peak at 1.16 Hz). Each frequency area was measured in milliseconds square (ms^2) (Gandhi & Rao, 2014; Lewis et al., 2014). The harmonic components are expressed in amplitude (in Volt/second or V.s unit), width (in Hertz or Hz unit) and surface or power (in square millisecond or ms2 unit). The PTG total power or PTG-TP is the sum of the 3 surfaces or powers of VLF, LF and HF.

2.5. Statistical Analysis

The objective of the study was to examine the ability of PTG-TP to detect insulin resistance (M-value <4.8). Statistical analysis was performed to correlate M-value and PTG-TP using the Spearman's coefficient. We compared groups by using Mann–Whitney U test. Receiver-operating characteristic curves were constructed to determine the specificity and sensitivity of PTG-TP in detecting M-value <4.8 $mg/kg_{ffm}\cdot min$. Data are reported as means ± SEM. A p-value <0.05 was considered statistically significant. Based upon the preliminary study results to have 90% power to detect a significant difference between insulin sensitivity subjects with the above mean and standard deviation at alpha = 0.05. Analyses was performed using MedCalc software for Windows (version 12.6.1, Ostend, Be).

3. Results

A total of 100 subjects, 30 lean, 42 overweight and 28 obese, classified according to BMI, were enrolled in the study. The mean BMI was 28.1 kg/m^2 (range 17.9–50.3). Baseline characteristics of the study subjects stratified by insulin resistance were shown in Table 1. IR as evaluated by HEC was presented in 23% of the subjects, which had an 4.8 $mg/kg_{ffm}\cdot min$. Women were presented at 15.8% of the IR prevalence, while men were presented 32.6%. The BMI, fat mass and PTG-TP were significantly higher for subjects with IR than those without IR (Table 1).

Fig. 3 depicts a moderate correlation between M-value and PTG-TP ($r = -0.64$, $p < 0.0001$), which were observed in Table 2 in comparison with distinct insulin resistance indices.

The ROC analysis 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 AUC = 0.929 for identifying insulin resistance (Fig. 4). In a separate ROC analysis, the women's group presented a sensitivity = 100.0%, specificity = 85.4% and AUC = 0.926 (cutoff >405.2); while the men's group was observed at a sensitivity = 92.9%, specificity = 82.8% and AUC = 0.933 (cutoff >406.2). All AUC ROC curve analysis were significant ($p < 0.0001$).

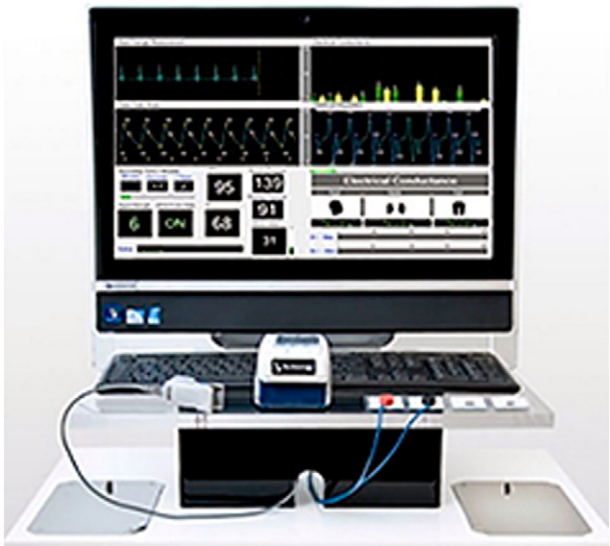

Fig. 1. ES Complex device; Integration of the ES complex software with the fingertip oximeter.

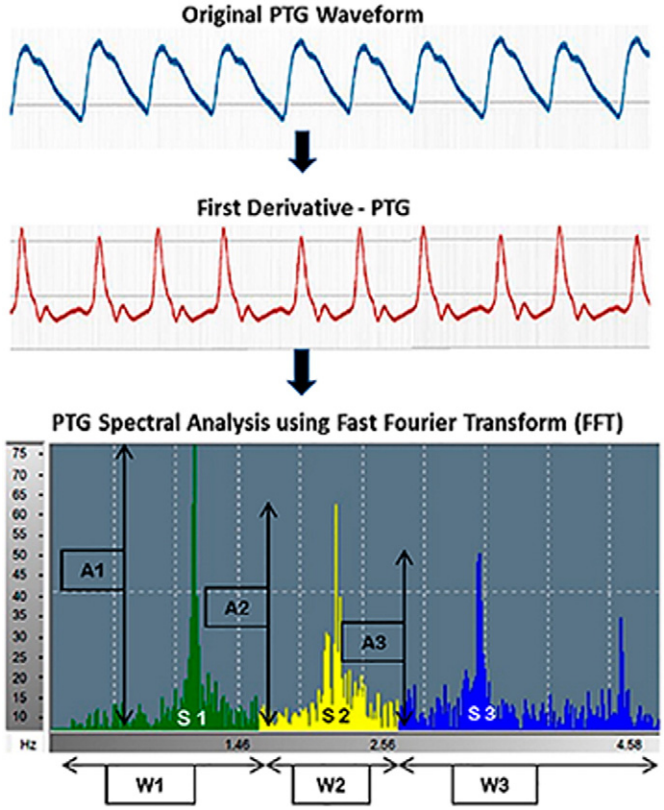

Fig. 2. PTG spectral analysis. A1 = amplitude very low frequencies (VLF), A2 = amplitude low frequencies (LF), A3 = amplitude high frequencies (HF). S1 = surface very low frequencies (VLF), S2 = surface low frequencies (LF), S3 = surface high frequencies (HF). W1 = width very low frequencies (VLF), W2 = width low frequencies (LF), W3 = width high frequencies (HF).

4. Discussion

Given the rising global burden of diabetes, and its impact on human health, society, economics, and public policy, the early diagnosis of this disease has become exceedingly important for its control and treatment. However, 45.8% of diabetic individuals go undiagnosed (Beagley, Guariguata, Weil, & Motala, 2014). This high prevalence of undiagnosed diabetics could be explained, among other

Table 1
Study participant characteristics in the groups with and without insulin resistance.

	M-value < 4.8	M-value > 4.8	p-value*
Number	23	79	-
Sex (male/female)	13/9	34/44	-
Age (years)	32,0 ± 1.9	33.5 ± 1.0	ns
Fasting plasma glucose (mmol/L)	4.8 ± 0.07	4.7 ± 0.03	ns
Hb1Ac (%)	5.6 ± 0.06	5.3 ± 0.04	0.001
Systolic blood pressure (mmHg)	124.5 ± 4.0	111.9 ± 1.6	0.001
Diastolic blood pressure (mmHg)	83.5 ± 2.7	74.3 ± 1.2	0.0001
Body mass index (kg/m^2)	34.5 ± 1.7	26.7 ± 0.5	<0.0001
Fat mass (%)	37.2 ± 1.5	29.3 ± 0.8	<0.0001
PTG-TP (m/s^2)	527.29 ± 24.15	327.7 ± 10.7	<0.0001

* p-value indicates comparison between those with (M-vale <4.8) versus without (M-value >4.8) insulin resistance.

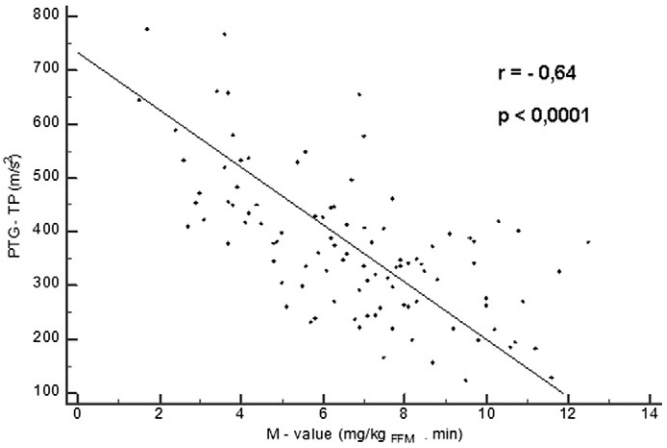

Fig. 3. Simple correlation between M-value (mg/kg_{ffm}·min) and photoplethysmographic Index, PTG-TP in 100 nondiabetic subjects. (r = −0.64; p < 0.0001; 95% confidence interval: −0.743 to −0.507).

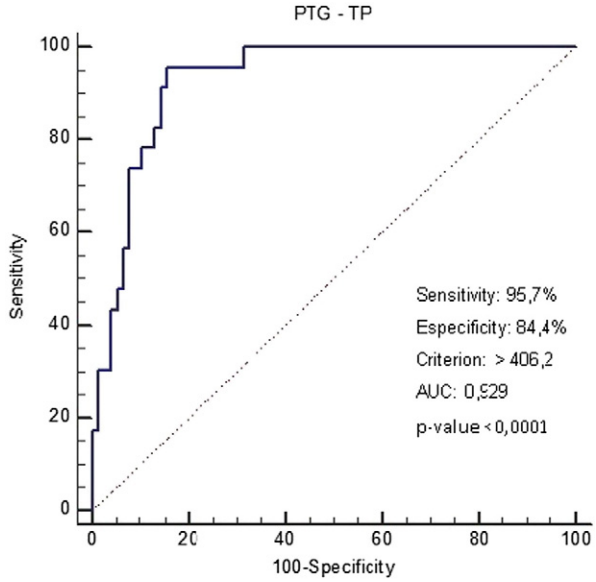

Fig. 4. ROC analyses of the utility of Photoplethysmographic Index, PTG-TP, for diagnosing insulin resistance. (n = 100) (standard error: 0.0247; 95% confidence interval: 0.860 to 0.971).

reasons, by the slow progression of T2DM. The slow onset and/or asymptomatic feature of DM leads individuals to perform diagnostic tests much later, when micro or macrovascular complications, such as retinopathy, nephropathy, and coronary artery disease, have appeared (Thompson et al., 1996). In order to perform earlier diagnosis of DM, the World Health Organization has recommended the development of methods and techniques for screening DM (WHO, 2003). Insulin resistance predicts the development of type 2 diabetes (Lillioja et al., 1993; Reaven, 1988). The increase of IR and beta cell dysfunction has been viewed as the trigger for the onset of T2DM (Ferrannini & Natali, 1991). Thus, an IR diagnosis could enable a medical intervention and/or changes to an individual's life style to prevent or delay the onset of T2DM.

Although several methods have been available for making definitive measurements for IR, the most accurate are in vivo assessments, including the intravenous glucose tolerance test with frequent samples (FSIVGTT) (Pacini & Bergman, 1986) and HEC - which are used as a reference for correlation and validation of other methods for IR assessment (George et al., 2011; Katz et al., 2000; Matsuda & DeFronzo, 1999). These techniques, however, are complicated, labor intensive, expensive and, in general, not suitable for large-scale studies or routine clinical work. The oral glucose tolerance test (OGTT) is another in vivo test, and it is the most often used to measure IR because it is simple, less expensive, and has a good correlation with the HEC (Cederholm & Wibell, 1990; Gutt et al., 2000; Hollenbeck, Chen, Chen, & Reaven, 1984; Mari, Pacini, Murphy, Ludvik, & Nolan, 2001; Matsuda & DeFronzo, 1999; Stumvoll et al., 2000). Surrogate measures of insulin sensitivity have been developed from OGTT. These indices correlate reasonably well with IR measured by the HEC (Cederholm & Wibell, 1990; Gutt et al., 2000; Mari et al., 2001; Matsuda & DeFronzo, 1999; Stumvoll et al., 2000). Besides the traditional in vivo methods to investigate IR, another index was developed to measure IR in large-scale studies. The HOMA-IR and QUICKI are the most used indices, because they are simple and have a good correlation with the HEC (Bonora et al., 2000; Katz et al., 2000). Although these methods are the most used in the IR assessment in epidemiological studies, they required a blood specimen for analysis; which may represent a limitation in some studies.

Various technologies have been developed and employed as alternatives to these methods. These technologies have been based on physiological variables - inputs derived through biosensors; variable interpretation and correlation through specific algorithms; and output assessment/diagnosis (Adami et al., 2012; Lewis et al., 2014). The PTG is an example of this technology, which has been successfully employed in the evaluation of endothelial dysfunction (Atkin, Laight, & Cummings, 2016; Gandhi & Rao, 2014; Kuvin et al., 2003). Given the relationship between insulin resistance and endothelial dysfunction, the PTG could be used in the assessment of IR.

In our study, adopting a cutoff M-value <4.8 mg/kg_{ffm}·min to detect IR, the overall prevalence of IR was 23% in subjects studied. This result is similar to the IR prevalence found in non-diabetics who were shown in the literature to be between 20 to 25% (DeFronzo & Ferrannini, 1991; Matsuda & DeFronzo, 1999; Reaven, 1988). Women had higher insulin sensitivity results than men; these results may be associated with gender differences in abdominal fat distribution, in which the standard gynoecia distribution and related to factors, such as higher adiponectinemia, promotes high insulin sensitivity (Deng & Scherer, 2010). The prevalence of IR in normal weight, overweight and obese subjects was 1, 8 and 12%, respectively. As an established relationship between IR and obesity (Ferrannini et al., 1997).

The ROC curve analysis results were very significant to evaluate the PTG-TP algorithm in IR diagnostic performance. The PTG-TP sensitivity and specificity overall results (sensitivity 95.7%, specificity =84.4%;

Table 2
Indexes to estimate insulin resistance/sensitivity and their correlation with hyperinsulinemic euglycemic clamp (HEC).

	Subjects	Correlation with HEC
OGTT derived indexes		
Hollenbeck et al. (1984)	NGT	r = 0.61. p = 0.001
Cederholm & Wibell (1990)	NGT, IGT, DM	r = 0.62. p < 0.0001
Gutt et al. (2000)	NGT, IGT, DM	r = 0.63. p < 0.001
Matsuda & DeFronzo (1999)	NGT, IGT, DM	r = 0.73. p < 0.0001
Belfiore et al. (2001))	NGT, O, ODM	r = 0.96. p < 0.001
Stumvoll et al. (2000)	NGT, IGT	r = 0.80. p < 0.0005
Mari et al. (2001)	IGT, DM, O, L	r = 0.73. p < 0.0001
Fasting insulin/glucose plasma indexes		
Homa-IR (Bonora et al., 2000)	ND	r = −0.75. p < 0.0001
Quicki (Katz et al., 2000)	NO, O, DM	r = 0.78. p < 2×10^{-12}
Photoplethysmography Index		
PTG-TP	NGT, IGT,O,OW,L	r = −0.64. p < 0.0001

OGTT = oral glucose tolerance test, NGT = normal glucose tolerance, IGT = impaired glucose tolerance, DM = type 2 diabetes, ND = non diabetic, O = obese, L = lean, OW = overweight, NO = non obese, HOMA-IR = homeostasis model assessment for insulin resistance, Quicki = quantitative insulin sensitivity check index, PTG-TP = photoplethysmography total power.

AUC_{ROC} = 0.929), and results by gender (women: sensitivity = 100%, specificity = 85.4%; AUC_{ROC} = 0,926; men: sensitivity = 92.9%, Specificity = 82.8%, AUC_{ROC} = 0.933) show better results compared to those obtained in other studies using consolidated methods and indices for IR assessment. For instance, Qu, Li, Rentfro, Fisher-Hoch, & McCormick (2011), using HOMA-IR to assess the IR in 1854 Americans of Mexican descent had a sensitivity of 64.1% and specificity of 81.8%, AUC_{ROC} = 0.809. In another study, Lee et al. (2006), analyzing different cutoffs in HOMA and Quick, had a 62.8% sensitivity and 65.7% specificity with AUC = 0.672 for HOMA, and sensitivity = 61.2% and specificity = 66.8%, AUC_{ROC} = 0.671 for a QUICKI. In a study of obese youth, George et al. (2011), comparing fasting insulin, HOMA-IR, Quick, and derived indices from OGTT obtained a AUC_{ROC} curve range from 0.888 to 0.946. Moreover, Maarek et al. (2015), study with 1096 subjects showed the reliability of spectral analysis of PTG to detect diabetic patients in a large group (respectively sensitivity and specificity of 78.5% and 90.2%).

In accordance with the aforementioned studies' data, the sensitivity, specificity and AUC_{ROC} found in PTG-TP IR screening, compared with the gold standard method, showed the significance and relevance of this new method as a practical screening tool in clinical practice and also for large-scale studies.

Indeed, our results showed a moderate correlation between HEC and the PTG-TP algorithm ($r = -0.64$, $p < 0.0001$). This correlation was similar to those found in the other IR studies (Belfiore, Iannello, Camuto, Fagone, & Cavaleri, 2001; Cederholm & Wibell, 1990; Gutt et al., 2000; Hollenbeck et al., 1984; Katz et al., 2000; Mari et al., 2001; Matsuda & DeFronzo, 1999; Stumvoll et al., 2000) (Table 2).

Our results could be explained in the relationship between the pathogenesis of insulin resistance, autonomic nervous system (ANS) and endothelial responses. In addition to the metabolic homeostasis, insulin plays an important role in haemodynamic homeostasis. At the cellular level, balance between phosphatidylinositol 3-kinase-(PI3K)-dependent insulin-signaling pathways that regulate endothelial NO production and mitogen activated protein kinase (MAPK)-dependent insulin-signaling pathways regulating the secretion of the vasoconstrictor endothelin-1 (ET-1) determines the vascular response to insulin. Diminished sensitivity to the vascular actions of insulin is typically accompanied by reduced PI3K-NO pathway and heightened MAPK-ET-1 pathway (Natali et al., 1997; Potenza, Addabbo, & Montagnani, 2009). These changes coupled with the metabolic abnormalities, that include glucotoxicity, lipotoxicity, and inflammation also lead to endothelial dysfunction. On the other hand, the hyperinsulinemia, present in IR state, was associated with increased sympathetic activity and attenuation of sympathetic/vagal balance; both processes, consequently, may lead to vascular dysfunction (Arcaro, 2002; Muscelli et al., 1998).

Thus, in IR state, autonomic and endothelial dysfunction, associated with the loss of insulin action, lead to changes in the PTG analysis, which was evaluated by the PTG-TP marker.

Although the PTG waveform is comprised of a pulsatile physiological waveform attributed to cardiac synchronous changes in the blood volume with each heartbeat and is superimposed on a slowly varying baseline with various lower frequency components attributed to respiration, sympathetic nervous system activity, and thermoregulation (Allen, 2007); the fact is that PTG-TP showed high specificity and sensitivity to detect insulin resistance in non-diabetic subjects in comparison with the HEC, independently the degree of IR of this study subjects.

The main clinical interest in IR detection is the prevention of T2DM, as well as its related diseases. The early diagnosis of IR could prevent or prolong the onset of T2DM, and it could positively impact the health of individuals, as well as control public health expenditures which are strongly impacted by T2DM. Although many methods have been proposed for screening individuals in the general population, the methods were always invasive, and required a minimum apparatus to execute. In this context, the PTG-TP marker, which uses only a pulse oximeter, has significant advantages in comparison with other methods. These advantages are: ease of use, non-invasive approach, no complex structure, and is extremely cost effective.

Considering an ROC curve analysis performance, our data suggest that PTG analysis, in comparison with the HEC gold standard, could be used alternatively to the classical methods of IR assessment, not to surrogate these methods, but as an efficient screening method.

Therefore, in 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.

Adverse Events

No adverse events are reported with the use of the device and during the HEC or PTG tests.

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