Orthostatic response in patients with type 2 diabetes mellitus evaluated through acceleration photoplethysmogram

José Federico Rivas-Vilchis1*, Eduardo Barrera-Escorcia2

1Universidad Autónoma Metropolitana, Unidad Iztapalapa, Departamento de Ciencias de la Salud, México.
2Universidad Anáhuac México, Campus Norte, Facultad de Ciencias de la Salud, Huixquilucan, Estado de México, México.

ID ORCID:
1https://orcid.org/0000-0002-7859-1993, 2https://orcid.org/0000-0003-3073-557X

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ABSTRACT

Introduction: One of the striking complications of diabetes mellitus is arterial circulatory dysfunction. The 30:15 ratio is an orthostatic index commonly used to diagnose circulatory alterations in diabetic patients with a long evolution. Indices obtained from the second derivative of photoplethysmogram (SDPPG) or acceleration photoplethysmogram (APG) characterize arterial pathological changes. Aim: To compare the cardiovascular response of non-diabetic subjects to active standing versus that of type-2 diabetes (DM2) patients using APG indices. Methods: Digital photoplethysmography (PPG) was obtained from healthy subjects (n = 15, age ± SD, 44.6 ± 7.2 years) and DM2 patients (n = 15, age ± SD, 48.3 ± 7.9 years). The 30:15 ratio, b/a, d/a, and APG-AI, all APG-based, of the participants were calculated and compared at baseline, 15 and 30 s. Results: Comparison of the 30:15 ratios between groups did not show a significant difference. No significant differences were observed between the APG indices in the two groups in the baseline period. However, d/a decreased, and APG-AI increased significantly at beat 30 after active standing in non-diabetic subjects. Values of APG indices in DM2 patients did not show significant changes. Conclusion: The results suggest that APG indices could be used to detect early vascular dysfunctions in DM2 patients.

Key words: orthostatism; acceleration photoplethysmogram indices; type 2 diabetes; arterial stiffness.
RESUMEN

Introducción: Una de las complicaciones de la diabetes mellitus es la disfunción circulatoria arterial. El coeficiente 30:15 es uno de los índices ortostáticos que se emplean para diagnosticar alteraciones circulatorias en diabéticos con evolución prolongada. Por otra parte, se emplean índices de la segunda derivada del fotoplettisograma (SDPPG) o fotoplettisograma por aceleración para caracterizar cambios patológicos de la función arterial. Objetivo: Comparar la respuesta cardiovascular a la bipedestación activa de sujetos sanos versus sujetos con diabetes tipo 2 mediante los índices de la SDPPG. Métodos: Se tomaron registros fotoplettisográficos digitales (PPG) en sujetos sanos (n = 15, edad ± DE, 44.6 ± 7.2 años) y sujetos con diabetes tipo 2 (n = 15, edad ± DE, 48.3 ± 7.9 años). Se calcularon los coeficientes 30:15, los índices b/a, d/a y SDPPG-IE en cada participante, basados en los componentes de la onda del SDPPG, y se compararon en el periodo basal y a los segundos 15 y 30. Resultados: Los coeficientes 30:15 de ambos grupos no mostraron diferencias significativas. Respecto a los índices SDPPG, no se observaron diferencias significativas entre los dos grupos en el periodo basal. Sin embargo, d/a disminuyó y SDPPG-IE aumentó, ambos en el latido 30 y de manera significativa después del ortostatismo activo en el grupo de sujetos sin diabetes. Los valores de los índices SDPPG en el grupo con diabetes tipo 2 no mostraron cambios significativos. Conclusión: Los resultados sugieren que los índices de la SDPPG pueden ser usados para detectar de manera temprana disfunciones vasculares en pacientes con diabetes tipo 2.

Palabras clave: ortostatismo; índices de la segunda derivada del fotoplettisograma; diabetes tipo 2; rigidez arterial.

INTRODUCTION

Type 2 diabetes mellitus (DM2) causes high morbidity, mortality, and high socioeconomic costs; it is estimated to affect more than 300 million people by 2030.1 Cardiovascular autonomic neuropathy as part of diabetic neuropathy is a frequent complication of types 1 and DM2 and leads to high mortality and morbidity.2, 3 Various tests are used to diagnose the cardiovascular component of cardiovascular autonomic neuropathy, such as heart rate variability, heart rhythm disorders, and the Ewing test.4 One of the best studied parameters of the Ewing test is the heart rate response to standing up or 30:15 ratio.5 A continuous recording of the heartbeat is obtained from when the subject stands up after lying down to obtain RR intervals. The 30:15 ratio is the coefficient of the RR intervals at beat 30 and beat 15, both with the subject already standing. A 30:15 ratio of ≥ 1.04 is considered normal.

The 30:15 ratio is also considered a criterion of the afferent (baroreceptor) and efferent parasympathetic function of the cardiac autonomic nervous system.6 Standing up from supine causes significant hemodynamic changes, such as decreased blood return to the heart, cardiac output, and blood pressure. The reduction in the pressure on the baroreceptors causes parasympathetic inhibition, and a compensatory sympathetic activation increases the heart rate and systemic vasoconstriction. Therefore, there is a change in the systolic and diastolic blood pressures.6

The acceleration photoplethysmogram (APG) is an optoelectronic tool that measures and records changes in the blood volume in a part of the body. Photoplethysmography (PPG) signals are applied in healthcare, including clinical, physiological, and vascular assessment, and research contexts as autonomic function.9 The second derivative of photoplethysmogram (SDPPG) or APG has characteristic traces that provide additional elements and a more sophisticated analysis of the PPG.10 The APG distinguishes five sequential waves called a, b, c, d, and e. From the relative heights of these waves, various ratios are obtained, such as b/a, d/a, and (b-c-d-e)/a or aging index (APG-AI), which are related to various physiological and pathophysiological variables such as age,14, 15, the compliance of the carotid artery,16, 17 blood pressure,18, coronary artery disease,19, and the presence of atherosclerotic disorders.15 In the early stages of DM2, the cardiovascular indices do not show significant changes, and it is until the stage of frank diabetic neuropathy that the 30:15 ratio decreases its values.17 Therefore, the purpose of this work was to determine whether the second derivative indices show changes in DM2 patients under orthostatic stress, even though diabetic neuropathy is not present yet.
METHODS

Two study groups were formed: one with 15 healthy subjects and another with 15 patients diagnosed with DM2, an evolution of ≤ 6 years, and oral glycemic control. All the participants were normotensive (blood pressure < 120/80 mmHg) at the time of the study; none had total serum cholesterol values > 200 mg/dl or electrocardiogram abnormalities. No subject had heart disease or was taking antihypertensive medication. The Toronto Clinical Neuropathy Score (TCNS) questionnaire was applied to DM2 patients to rule out the presence of polyneuropathy\textsuperscript{18}, while a physical examination was also carried out to rule out lower limb abnormalities as sensitivity, strength, and abnormal ankle reflex. Subjects were studied fasting and abstaining from caffeine, alcohol, and tobacco use 24 h before the study. The Ethics Committee of the Biological and Health Sciences Division at the Iztapalapa Unit, Autonomous Metropolitan University approved the study. Additionally, the ethical principles for medical research with human beings of the World Medical Association (WMA) of the Declaration of Helsinki (2013) were followed, and all participants gave their written informed consent. The recordings were made in a laboratory with a temperature of 23 °C ± 1 °C. All subjects were allowed to rest and acclimatize for at least 30 min before the start of the recordings.

PPG registration. The PPG detects changes of light absorption by hemoglobin, which reflects changes in blood flow volume. A photoplethysmography transducer (TSD 200; BIOPAC Systems, Goleta, CA, USA) that transmits infrared light at 860 ± 90nm was used to obtain the PPG (Figure 1). The transducer was placed on the index finger of the right hand of each experimental subject. The frequency response of the photoplethysmograph was flat at 10 Hz. The PPG curve with a frequency of 200 points per second was recorded through a 12-bit analog-digital converter. Acknowledge v3.8.1 (MP100; BIOPAC Systems, Goleta, CA, USA) was used as analysis platform.

SDPPG registration. The SDPPG was obtained using Origin v7.5 (Microcal Software, Inc., Northampton, MA, USA). The d2PPG/dt2 or APG wave typically comprises five distinct waves from a to e: positive waves a, c, and e; negatives b and d. The b/a ratio is calculated with the quotient of relative values b and a; the d/a ratio is calculated with the quotient of relative values of waves d and a. The aging index (APG-AI) was defined as the quotient of the algebraic sum of (b-c-d-e) divided by a.

The zero start time of the analyses was considered when the participant was fully standing. Once the person stood up, the RR intervals were measured at beats 15 and 30; the RR30/RR15 ratio or 30:15 ratio was calculated using these values. Values 30:15 > 1.04 were considered normal, those between 1.01 and 1.03 were limits of normality, and values < 1.00 were considered abnormal\textsuperscript{17}.

STATISTICAL ANALYSIS

The records of the subjects were plotted using Plot2 (Michael Wesemann, Berlin, Germany, 2019). The interpolated data of the set of 15 subjects in each group were averaged and the kinetic curves of the RR intervals were obtained. Baseline values were compared with those corresponding to beats 15 and 30 using a two-tailed t-test. Data are reported as mean ± standard deviation (SD) and analyzed using SPSS Statistics v22.0 (Chicago, USA). Data are presented as mean ± SD. The chosen level of statistical significance was p < 0.05.

RESULTS

The characteristics of healthy subjects and DM2 patients are shown in Table 1. The demographic and physiological data were not significantly different between the two study groups. None of the DM2 patients obtained ≥ 5 points in the TCNS questionnaire.
The comparison of the 30:15 ratio of healthy subjects (1.125 ± 0.13, mean ± SD) versus that of DM2 patients (1.139 ± 0.07, mean ± SD) showed no significant differences (p = 0.7802).

**SDPPG indices**

Figure 1 shows typical traces of the PPG or volume of the digital pulse and SDPPG. Table 2 shows the APG indices in healthy subjects at baseline and beats 15 and 30. The d/a index was significantly reduced, and the APG-AI significantly increased at beat 30 in both cases, p = 0.02 and p = 0.04, respectively.

The SDPPG indices in DM2 patients at baseline and beats 15 and 30 are shown in Table 3. Comparing the three periods, none of the indices showed a significant difference concerning the baseline values.

**DISCUSSION**

The noteworthy findings of this study were that the 30:15 ratios did not show significant differences between groups. Before the active standing test, the APG indices evidenced no significant differences between the two groups in the b/a, d/a, and APG-AI indices. However, d/a decreased, and APG-AI increased significantly in healthy subjects at beat 30 after standing up. On the other hand, the APG indices in DM2 patients did not show significant changes in the periods corresponding to beats 15 and 30 as compared to the baseline values.

The d/a index is related to vasoactive drugs and metabolic syndrome; it has also been proposed as a predictor of cardiovascular events. The d wave occurs in the late systolic phase of PPG and is strengthened by the retrograde wave from the periphery. Therefore, the d/a ratio correlates significantly with the central augmentation index and represents the...
structural and functional properties of the systemic arterial tree, including peripheral circulation. 

The rate of pressure increase is also related to central arterial pressure. The d/a index is associated with the reflected wave component of the aortic arterial pressure; then, the d/a index is an indirect clue of arterial stiffness. Consequently, the d/a index reflects the functional properties of peripheral circulation and is also related to peripheral vascular resistance. Furthermore, the APG-AI index correlates with age and can help to assess vascular aging and atherosclerotic disease. The absence of changes in d/a and APG-AI indices observed in DM2 patients under orthostatic stress may indicate an initial lacking response due to arterial stiffness.

CONCLUSIONS

In conclusion, the comparison of 30:15 ratios of healthy subjects against those of type 2 diabetes patients did not show significant differences. However, the acceleration photoplethysmogram aging and d/a indices showed differences between groups at beat 30. Our results suggest that circulatory disturbances anticipate other components of diabetic neuropathy. Trials with a more significant number of participants and people with diabetic neuropathy will establish whether acceleration photoplethysmogram indices can be used in the early detection of diabetic neuropathy.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest regarding the content of this manuscript.

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