Proceedings of Scientific Research Universidad Anáhuac, 2021, 1(2): 5-10.
ISSN: in process.

Research Article

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

José Federico Rivas-Vilchis[a1]*, Eduardo Barrera-Escorcia[b2]

[a]Universidad Autónoma Metropolitana, Unidad Iztapalapa, Departamento de Ciencias de la Salud, México.
[b]Universidad Anáhuac México, Campus Norte, Facultad de Ciencias de la Salud, Huixquilucan, Estado de México, México.

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

https://doi.org/10.36105/psrua.2021v1n2.01

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.

* *Corresponding author*: José Federico Rivas Vilchis. Universidad Autónoma Metropolitana, Unidad Iztapalapa, Departamento de Ciencias de la Salud. Av. San Rafael Atlixco 186, Alcaldía Iztapalapa, Ciudad de México, C.P. 09340. Tel.: +52 55 5804 4920. Email: jfrv@xanum.uam.mx

Received: 4 April 2021.
Accepted: 7 June 2021.

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 fotopletismograma (SDPPG) o fotopletismograma 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 fotopletismográficos 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 período 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 fotopletismograma; 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 a supine position produces an integrated reflex response of the cardiovascular system, including changes in heart rate and blood pressure.[6] This response to circulatory stress elicited by standing up requires the proper functioning of diverse and complex mechanisms of the cardiovascular system. The autonomic nervous system (ANS) is the primary mechanism of the immediate responses to changes in position, and the renin-angiotensin-aldosterone system, which is also a component of this response, acts in the longer term.[7]

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.[8]

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, e, and f. 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[11, 12], the compliance of the carotid artery[13], blood pressure[14], coronary artery disease[15], and the presence of atherosclerotic disorders.[16] 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.

https://doi.org/10.36105/psrua.2021v1n2.01

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[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 f. The APG indices are calculated using the relative height of the positive or negative inflections. The values of b wave and d wave are normalized to a wave, then the ratios b/a and d/a are obtained. The APG-AI is defined as the quotient of the algebraic sum /b-c-d-e waves normalized with a wave value 10 (see Figure 1). The APG indices of the basal values in each group were compared versus the periods corresponding to beats 15 and 30.

30:15 ratio. To obtain the 30:15 ratio, the participant remained in supine position for a stabilization period of 10 min. The photoplethysmographic recording lasted 2 min. Each participant stood up unaided at the end of the first minute of recording.

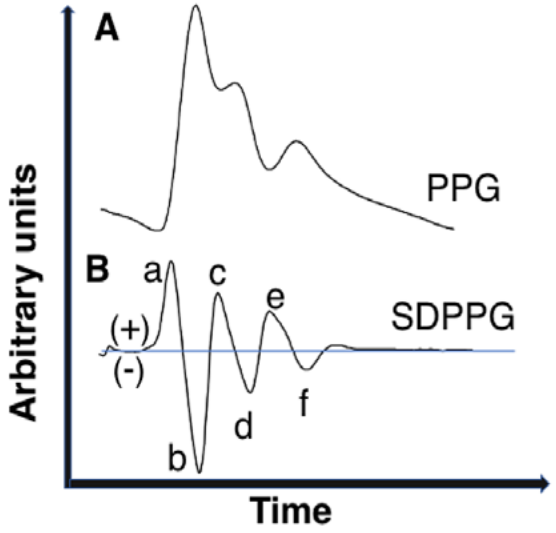

FIGURE 1. Representative trace of the digital volume pulse and second derivative of photoplethysmogram (SDPPG).

The SDPPG or acceleration photoplethysmogram wave is made up of five components from wave 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.[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.

Index 30:15

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[10] and metabolic syndrome[20]; it has also been proposed as a predictor of cardiovascular events.[19] 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

Table 1. Demographic and clinical data of the study groups.

Demographic and clinical parameters	Controls	Type 2 diabetes patients
n (women)	15 (4)	15 (9)
Age (years ± SD)	44.6 ± 7.2	48.3 ± 7.9
Diastolic pressure (mmHg)	123 ± 12.2	128 ± 14.1
Systolic pressure (mmHg)	74.1 ± 9.2	76.3 ± 10.5
Heart rate (beats/min)	74.5 ± 8.2	75.4 ± 9.4

Data are mean ± standard deviation.

Table 2. Indices of second derivative of photoplethysmogram wave in basal periods and at beats 15 and 30 after active standing in healthy subjects.

Index	Basal	Beat 15	Beat 30
b/a	–0.81 ± 0.11	–0.78 ± 0.12	–0.74 ± 0.14
d/a	–0.17 ± 0.15	–0.24 ± 0.14	–0.39 ± 0.12*
APG-AI	–0.86 ± 0.28	–0.79 ± 0.21	–0.62 ± 0.16*

Data are mean ± standard deviation. * p < 0.05; APG-AI = aging index defined as (b-c-d-e)/a; b/a = quotient of the relative values of the height of b-wave and a-wave; d/a = quotient of the relative values of the height of d-wave and a-wave.

Table 3. Second derivative indices of the photoplethysmogram wave at baseline and at beats 15 and 30 after active standing in type 2 diabetes patients.

Index	Basal	Beat 15	Beat 30
b/a	–0.73 ± 0.10	–0.70 ± 0.15	–0.67 ± 0.14
d/a	–0.23 ± 0.15	–0.27 ± 0.14	–0.33 ± 0.12
APG-AI	–0.74 ± 0.28	–0.69 ± 0.19	–0.64 ± 0.16

Data are mean ± standard deviation. * p < 0.05; APG-AI = aging index defined as (b-c-d-e)/a; b/a = quotient of the relative values of the height of b-wave and a-wave; d/a = quotient of the relative values of the height of d-wave and a-wave.

https://doi.org/10.36105/psrua.2021v1n2.01

structural and functional properties of the systemic arterial tree, including peripheral circulation.[20]

The rate of pressure increase is also related to central arterial pressure.[21,22] 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.[19] Consequently, the d/a index reflects the functional properties of peripheral circulation and is also related to peripheral vascular resistance.[20] Furthermore, the APG-AI index correlates with age[10] and can help to assess vascular aging and atherosclerotic disease.[23,24] The absence of changes in d/a and APG-AI indices here observed in DM2 patients under orthostatic stress may indicate an initial lacking response due to arterial stiffness.[25,26]

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.

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047-53.
   http://doi: 10.2337/diacare.27.5.1047
2. Yun JS, Park YM, Cha SA, Ahn YB, Ko SH. Progression of cardiovascular autonomic neuropathy and cardiovascular disease in type 2 diabetes. Cardiovasc Diabetol. 2018;17(1):109.
   http://doi: 10.1186/s12933-018-0752-6
3. Breder ISS, Sposito AC. Cardiovascular autonomic neuropathy in type 2 diabetic patients. Rev Assoc Med Bras. (1992). 2019;65(1):56-60.
   http://doi: 10.1590/1806-9282.65.1.56
4. Lin K, Wei L, Huang Z, Zeng Q. Combination of Ewing test, heart rate variability, and heart rate turbulence analysis for early diagnosis of diabetic cardiac autonomic neuropathy. Medicine (Baltimore). 2017;96(45):e8296.
   http://doi: 10.1097/MD.0000000000008296
5. Spallone V, Bellavere F, Scionti L, et al. Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. Nutr Metab Cardiovasc Dis. 2011;21:69-78.
   http://doi: 10.1016/j.numecd.2010.07.005
6. Borst C, Wieling W, van Brederode JF, Hond A, de Rijk LG, Dunning AJ. Mechanisms of initial heart rate response to postural change. Am J Physiol.1982;243(5):H676-81.
   http://doi: 10.1152/ajpheart.1982.243.5.H676
7. Freeman R, Abuzinadah AR, Gibbons C, Jones P, Miglis MG, Sinn DI. Orthostatic Hypotension: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018;72(11):1294-1309.
   http://doi: 10.1016/j.jacc.2018.05.079
8. Furlan R, Porta A, Costa F, Tank J, Baker L, Schiavi R, Robertson D, Malliani A, Mosqueda-Garcia R. Oscillatory patterns in sympathetic neural discharge and cardiovascular variables during orthostatic stimulus. Circulation. 2000;101(8):886-92.
   http://doi: 10.1161/01.cir.101.8.886
9. Gonzales R, Manzo A, Delgado J, Padilla JM, Trenor B, Saiz J. A computer base photoplethysmographic vascular analyser through derivatives. Comp Cardiol. 2008; 35:177-80.
   http://doi: 10.1109/CIC.2008.4749006
10. Takazawa K, Tanaka N, Fujita M, Matsuoka O, Saiki T, Aikawa M, et al. Assessment of vasoactive agents and vascular aging by the second derivative of photoplethysmogram waveform. Hypertension. 1998;32:365–70.
    http://doi: 10.1161/01.hyp.32.2.365
11. Hashimoto J, Watabe D, Kimura A, Takahashi H, Ohkubo T, Totsune K, Imai Y. Determinants of the second derivative of the finger photoplethysmogram and brachial-ankle pulse-wave velocity: the Ohasama study. Am J Hypertens. 2005;18(4 Pt 1):477-85.
    http://doi: 10.1016/j.amjhyper.2004.11.009
12. Ohshita K, Yamane K, Ishida K, Watanabe H, Okubo M, Kohno N. Post-challenge hyperglycaemia is an independent risk factor for arterial stiffness in Japanese men. Diabet Med. 2004;21:636-39.
    http://doi: 10.1111/j.1464-5491.2004.01161.x
13. Imanaga I, Hara H, Koyanagi S, Tanaka K. Correlation between wave components of the second derivative of plethysmogram and arterial distensibility. Jpn Heart J 1998; 39:775-84.
    http://doi: 10.1536/ihj.39.775
14. Hashimoto J, Chonan K, Aoki Y, Nishimura T, Ohkubo T, Hozawa A, et al. Pulse wave velocity and the second

derivative of the finger photoplethysmogram in treated hypertensive patients: their relationship and associating factors. J Hypertens. 2002;20:2415-22.

http://doi: 10.1097/00004872-200212000-00021

15. Otsuka T, Kawada T, Katsumata M, Ibuki C. Utility of second derivative of the finger photoplethysmogram for the estimation of the risk of coronary heart disease in the general population. Circ J. 2006;70:304-10.

http://doi: 10.1253/circj.70.304

16. Bortolotto LA, Blacher J, Kondo T, Takazawa K, Safar ME. Assessment of vascular aging and atherosclerosis in hypertensive subjects: second derivative of photoplethysmogram versus pulse wave velocity. Am J Hypertens. 2000;13:165-71.

http://doi: 10.1016/s0895-7061(99)00192-2

17. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care. 1985;8(5):491-8.

http://doi: 10.2337/diacare.8.5.491

18. Abraham A, Barnett C, Katzberg HD, Lovblom LE, Perkins BA, Bril V. Toronto Clinical Neuropathy Score is valid for a wide spectrum of polyneuropathies. Eur J Neurol. 2018;25(3):484-90.

http://doi: 10.1111/ene.13533

19. Kawada T, Otsuka T. Factor structure of indices of the second derivative of the finger photoplethysmogram with metabolic components and other cardiovascular risk indicators. Diabetes Metab J. 2013;37(1):40-5.

http://doi: 10.4093/dmj.2013.37.1.40

20. Otsuka T, Kawada T, Katsumata M, Ibuki C, Kusama Y. Independent determinants of second derivative of the finger photoplethysmogram among various cardiovascular risk factors in middle-aged men. Hypertens Res. 2007;30(12):1211-8.

http://doi: 10.1291/hypres.30.1211

21. Munir S, Guilcher A, Kamalesh T, Clapp B, Redwood S, Marber M, Chowienczyk P. Peripheral augmentation index defines the relationship between central and peripheral pulse pressure. Hypertension. 2008;51(1):112-8.

http://doi: 10.1161/HYPERTENSIONAHA.107.096016

22. Kohjitani A, Miyata M, Iwase Y, Sugiyama K. Responses of the second derivative of the finger photoplethysmogram indices and hemodynamic parameters to anesthesia induction. Hypertens Res. 2012;35(2):166-72.

http://doi: 10.1038/hr.2011.152

23. Kimura Y, Takamatsu K, Fujii A, Suzuki M, Chikada N, Tanada R, Kume Y, Sato H. Kampo therapy for premenstrual syndrome: efficacy of Kamishoyosan quantified using the second derivative of the fingertip photoplethysmogram. J Obstet Gynaecol Res. 2007;33(3):325-32.

http://doi: 10.1111/j.1447-0756.2007.00531.x

24. Tabara Y, Igase M, Okada Y, Nagai T, Miki T, Ohyagi Y, Matsuda F, Kohara K. Usefulness of the second derivative of the finger photoplethysmogram for assessment of end-organ damage: The J-SHIPP study. Hypertens Res. 2016;39(7):552-6.

http://doi: 10.1038/hr.2016.18

25. Kannenkeril D, Bosch A, Harazny J, Karg M, Jung S, Ott C, Schmieder RE. Early vascular parameters in the micro- and macrocirculation in type 2 diabetes. Cardiovasc Diabetol. 2018;17(1):128.

http://doi: doi: 10.1186/s12933-018-0770-4

26. Drinkwater JJ, Chen FK, Brooks AM, Davis BT, Turner AW, Davis TME, Davis WA. The association between carotid disease, arterial stiffness and diabetic retinopathy in type 2 diabetes: the Fremantle Diabetes Study Phase II. Diabet Med. 2021;38(4):e14407.

http://doi: doi: 10.1111/dme.14407

https://doi.org/10.36105/psrua.2021v1n2.01