RESEARCH ARTICLE

The value of concomitant testing of cutaneous silent period with sympathetic skin response and heart rate variability in Type-2 diabetes patients: An electrophysiological study

Aya Falah Alrekabi, Safaa Hussein. Alshemmari

Abstract

Objective: To explore the association among cutaneous silent period, sympathetic skin response and heart rate variability in diabetes patients.

Method: The case-control study was conducted at the Department of Physiology, College of Medicine, Al-Mustansiriyah University, Baghdad, Iraq, from November 1, 2020, to May 20, 2021, and comprised 24 healthy controls in Group I and 49 patients of type 2 diabetes in Group II who were recruited from the neuro-electrophysiological unit of Al-Imamain Al-Kadhmean Teaching Hospital, Baghdad, Iraq. Both groups were subjected to cutaneous silent period, sympathetic skin response and heart rate variability testing. Data was analysed using SPSS 24.

Results: Of the 73 subjects, 24(32.9%) were in Group I and 49(67.1%) were in Group II. Cutaneous silent period mean latency values were significantly increased in Group II compared to Group I ($p<0.05$), and a negative sympathetic skin response in the right lower limb was significantly different between the groups ($p<0.001$). There was no significant correlation between Cutaneous silent period and sympathetic skin response values ($p>0.05$). Heart rate variability was significantly increased in diabetic patients with negative sympathetic skin response compared to those with positive sympathetic skin response ($p<0.05$).

Conclusion: Simultaneous measurement of cutaneous silent period, sympathetic skin response and heart rate variability should be done as there were no strong correlation among the tests in diabetic patients.

Key Words: Diabetes, Heart, Extremity,

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Introduction

Small fibre neuropathy (SFN) is caused by damage of non-myelinated type C and thinly-myelinated type A delta fibre[1]. Diabetes mellitus (DM) is a common cause of SFN. Despite the fact that distal symmetrical polyneuropathy is the most prevalent kind of diabetic peripheral neuropathy (DPN), tiny fibres are frequently involved in the early stages of the disease, and symptoms caused by their dysfunction usually dominate the clinical presentation. DPN affects about 30-50% of diabetics and is categorised into two types: generalised distal symmetrical polyneuropathy and focal/multifocal neuropathy[2]. The suppression of an ongoing muscle contraction following noxious digital stimulation is called cutaneous silent period (CSP), which is influenced by several physiological factors[3]. It is an oligosynaptic nociceptive reflex that has been known for a long time[4]. Determination of CSP is of great value in the assessment of SFN[5]. The latency and duration of CSP in the upper limb in the small-diameter fibre polyneuropathy did not show significant changes in a study, while the latency of the lower limb was prolonged in patients with pain compared to the corresponding value among patients without pain or healthy subjects[6].

Sympathetic skin response (SSR) is a non-invasive diagnostic tool used to assess the function of the sympathetic nervous system that detects the electrical potential of the skin evoked by internal or external stimuli[7]. One of the practical testing of the parasympathetic activity is heart rate variability (HRV) based on sinus arrhythmia using a programmed electromyography (EMG) machine[8]. Parasympathetic innervation is responsible for beat-to-beat variation in heart rate with respiration. Inhalation temporarily suppresses vagal activity during the respiratory process, resulting in an increase in the heart rate. Exhalation causes vagal activity to resume which then decreases the heart rate. During expiration, the R-R interval is the longest, whereas during inspiration, it is the shortest[9]. A significant HRV increment was observed in diabetic patients, which was more pronounced with concomitant hypertension (HTN), indicating that the sympathovagal

Department of Physiology, Mustansiriyah University, Baghdad, Iraq.

Correspondence: Aya Falah Alrekabi

Email: ayaalijana@gmail.com

balance was shifted to the dominant parasympathetic activity[10].

The current study was planned to explore the association among CSP, SSR and HRV done simultaneously in type 2 DM (T2DM) patients.

Patients and Methods

The case-control study was conducted at the Department of Physiology, College of Medicine, Al-Mustansiriyah University, Baghdad, Iraq, from November 1, 2020, to May 20, 2021, and comprised healthy controls in Group I and T2DM patients in Group II who were recruited from the neuro-electrophysiological unit of Al-Imamain Al-Kadhmean Teaching Hospital, Baghdad, Iraq. The sample was raised using consecutive nonprobability sampling technique after approval from the institutions ethics review committee, and written informed consent from all the participants. Those included were T2DM patients of either gender aged ≥40 years regardless of disease duration and glycaemic indices. The control group was matched for age and gender. Patients with a previous diagnosis of neurological, neuro-muscular, cardiovascular, renal and hepatic diseases were excluded. Those using drugs related to beta-adrenoceptor activating or blocking agents, calcium entry blockers, antiarrhythmic drugs, and nerve stabilising agents currently or within the preceding 4 weeks were also excluded.

All the subjects were examined thoroughly, and the body mass index (BMI) was calculated using the standard WHO formula:

BMI (kg/m^2) = (Weight (kg))/(Square height (m)) .

The result was assessed by the recommended values by WHO: underweight (score of under 18.5 kg/m2), normal (18.5-24.9 kg.m2), overweight (25-29.9 kg.m2) and obese (over 30 kg.m^{-2})[11].

The results were categorised as underweight, normal, overweight or obese accordingly.

The glycaemic indices included fasting blood glucose (FBG) and glycosylated haemoglobin (HbA1c). Controlled T2DM was defined as HbA1c up to 7% and uncontrolled diabetes as HbA1c >7%[12]. Upper limb CSP was recorded from the right abductor polices brevis (APB) muscle. The second digit was stimulated with ring electrodes. EMG activity was recorded using surface electrodes from the APB to obtain steady maximal contraction. An EMG audio signal was used to monitor muscle contraction and the individual was requested to perform maximum contraction against resistance. A single stimulus of 0.5 millisecond duration and 80 milliampere intensity was applied to the second digit during maximal voluntary contraction until a complete silent period of reliable latency and duration was achieved[6].

SSR was recorded when the active electrode was put in the right palm or sole and the reference over the dorsum of the respective body part. Then, median and tibial nerves were stimulated and recording was obtained from the palm and sole respectively[7].

HRV was measured using a surface recording disk electrode that was fixed to the left anterior chest area at the 4th and 5th intercostal spaces, a reference electrode was fixed to the left anterior axillary line over the 5th or 6th rib, and a ground electrode was placed on the midline of the sternum while the patient was at rest in a supine position with head elevated to 30 degrees. To display the QRS complexes on the screen, the oscilloscope's sensitivity and sweep speed were adjusted; the R peak was in the negative direction. The first complex was the triggering potential, and the time variation of the second complex was the variation in the R-R interval. The test was based on the phenomenon of respiratory arrhythmia, which is most evident at a breathing rate of 6 breaths per minute (BPM). The subject was asked to relax and breathe normally for 1min at which point the heart beats were recorded. Then the subject was asked to take deep breaths at 6BPM, with 5 seconds of inhalation and 5 seconds of exhalation per breath. The heart beats were recorded again at 1 and 2 minutes of breathing[8].

Data was analysed using SPSS 24. Data was presented as frequencies and percentage, median and interquartile range, and mean ± standard deviation, as appropriate. Two-tailed independent two-sample t-test was used for continuous variables, and Fisher Exact probability test for categorical variables. Correlations among the variables were tested using Pearson (rho) correlation test. P≤ 0.05 was taken as significant.

Results

Of the 73 subjects, 24(32.9%) were in Group I and 49(67.1%) were in Group II. CSP mean latency values were significantly increased in Group II compared to Group I ($p<0.05$), and a negative SSR in the right lower limb was significantly different ($p<0.001$). HRV was not significantly different between the groups (Table 1).

There was non-significant correlation of CSP latency with positive SSR latency and HRV during deep breathing (Table 2).

Patients with negative SSR had prolonged latency-1 and latency-2 compared to those who showed positive SSR

Table-1: Electrophysiological analyses..

Tests	Group I (n=24)	Group II (n=49)	p-value
Cutaneous silent period			
Latency-1 (ms)	71.1 ±8.9	83.8±12.3	<0.001
Latency-2 (ms)	114.7 ±8.2	129.1±15.4	<0.001
Sympathetic skin response			
Positive response			
Upper right limb			
Latency (ms)	1.445±0.231	1.512±0.221 (n-46)	0.231
Amplitude (mV)	3.369±2.031	3.081±2.496 (n=46)	0.617
Lower right limb			
Latency (ms)	2.227±0.351	2.243±0.455 (n=31)	0.891
Amplitude (mV)	2.177±1.282	3.924±3.965 (n=31)	0.133
Negative response (No.)			
Upper right limb	0	3	0.546
Lower right limb	0	18	<0.001
Heart rate variability (beats/min)			
Baseline	72.7±9.8	73.0±15.1	0.921
1-min after deep breathing	73.5±9.0 (p=0.439)	76.1±17.3 (p=0.014)	0.408
2-min after deep breathing	73.1±8.1 (p=0.130)	76.7±16.2 (p=0.003)	0.270

Table-2: Correlation of cutaneous silent period (CSP) values with sympathetic skin response (SSR) and heart rate variability (HRV) values in type 2 diabetes patients

Test	Cutaneous silent period	
	Latency-1	Latency-2
Positive sympathetic skin response		
Upper right limb (Latency (ms)	-0.083 (0.588)	-0.088 (0.565)
Lower right limb (Latency (ms)	0.326 (0.090)	0.078 (0.693)
Heart rate variability (beats/min)		
Baseline	-0.017 (0.910)	-0.075 (0.616)
1-min after deep breath	-0.127 (0.395)	-0.133 (0.373)
2-min after deep breath	-0.173 (0.245)	-0.217 (0.143)

The results are presented as correlation calculated by Pearson (rho) test and (p-value)

Table-3: Comparison of cutaneous silent period (CSP) and heart rate variability (HRV) values in type 2 diabetes patients with and without sympathetic skin response (SSR)..

Tests	Sympathetic skin response		p-value
	Positive response	Negative response	
Cutaneous silent period			
Latency-1 (ms)	81.7±14.9	127.0±13.6	0.260
Latency-2 (ms)	86.9±15.6	132.0±17.6	0.282
Heart rate variability (beats/min)			
Baseline	70.1±14.7	777.2±15.0	0.109
1-min after deep breath	71.6±13.7	82.5±19.9	0.042
2-min after deep breath	73.5±14.2	81.5±18.3	0.168

(Table 3). HRV was higher in patients with negative SSR, which increased by 1.5BPM after 1 minute of deep breathing in positive SSR subjects compared to 5.3BP< in those with a negative SSR (p=0.042).

Discussion

Diabetic SFN is extremely difficult to detect clinically due to limited objective procedures. Findings of neurological examination and complaints are considered the cornerstone of SFN diagnosis. Routine nerve conduction studies (NCS), however, can only show large fibre function, and small fibre dysfunction has to be recorded using a variety of techniques, such as CSP and SSR and HRV measurement[13].

The present study showed that diabetic patients had significant abnormal values in these 3 different tests, indicating evidence of different types of neuropathies. The study found that the CSP latency was prolonged in T2DM patients with a mean disease duration of 9.3 years, which agreed with a recent study that reported the latency of CSP was prolonged in T2DM patients with duration of the disease up to 10 years[14]. Moreover, the current findings significantly confirmed that CSP is a useful discriminating test of diabetes with small-diameter fibres from healthy subjects [15]. Negative SSR was found in 18(36.7) diabetic patients in the current study, which was I line with a study that reported 37%[16]. The age of the patient could affect the impairment of SSR as the skin blood flow decreases with aging, and the current patients had significantly higher mean age compared to the healthy subjects. A significant HRV increment after deep breathing in T2DM patients indicates the predominance of parasympathetic activity[17].

The fundamental finding of the current study was that there were no correlations among the results of the 3 tests. However, there was promising HRV data in patients with impaired SSR. The findings agreed with another study that showed an uneven distribution of SSR, CSP and HRV in asymptomatic neurological T2DM, and recommended performing all electrophysiological tests to diagnose early neuropathy[18]. A significant association of SSR impairment and HRV is an important finding because there is evidence that these measurements are not suitable for the assessment of the autonomic nervous system (ANS) function in pathological conditions[19]. Therefore, concomitant measurement of CSP, SSR and HRV is an important diagnostic tool of somatic or autonomic neuropathy[20]

Limitations: The current study has limitations as the sample size was small, and it was not calculated which could have affected the power of the study.

Conclusion

Simultaneous measurement of CSP, SSR and HRV should be done as there were no strong correlation among the tests in diabetic patients.

Disclaimer: None.

Conflict of Interest: None.

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