PAIN-RELATED EVOKED POTETIAL IN PATIENTS WITH DIABETES TYPE 2

Do Duy Giang[1,*], Nguyen Huy Binh[1], Le Dinh Tung[1,]**

ABSTRACT

Background: *Small-fiber peripheral neuropathy (SFN) is one of common complications in diabetes. The utility of pain – related evoked potential (PREP) stimulated by concentric electrode in initial finding of diabetic small-fiber neuropathy was taken into investigation in this study.* ***Methods:*** *50 healthy adults as well as 23 patients with diabetes type 2 without neuropathic symptoms and 27 patients with diabetes and neuropathic symptoms over 50 years old were included. All subjects were recorded PREP by Neuropack MEB-9400 S1 Series EMG/NCV/EP Measuring System.* ***Results:*** *After stimulation, nearly all subjects depicted a negative wave followed by a positive wave (73/100 subjects). Besides, 13 subjects showed a positive wave with two peaks, 3 subjects presented a unique positive wave and only one displayed a negative wave with two peaks. In patients without neuropathic symptoms, there were significant decreasing of PREP amplitudes and increasing of latencies elicited from lower limbs (latency: 221.6 ± 20.4 ms and amplitude: median 23.39 μV, p < 0.001). In neuro-symptomatic diabetic patients, there were abnormalities from both upper limbs (latency: 18.7 ± 30 ms and amplitude: median 23.35 μV, p < 0.001) and lower limbs (latency: 234.5 ± 20.8 ms and amplitude: median 16.63 μV, p < 0.001).* ***Conclusion:*** *These results submitted that the procedure of pain – related evoked potentials stimulated by concentric electrode may supply to early detection of diabetic small fiber neuropathy.*

Key words: *pain-related evoked potentials, diabetes.*

1. INTRODUCTION

Peripheral neuropathy is one of common complications and represents major causes of food ulcers and amputation in diabetes [7]. The early recognition can base on clinical tests and electrophysiological testing involve assessment of large-fiber (Aα and Aβ) and small-fiber (Aδ and C) function [1]. Routine nerve conduction study (NCS) and electromyography (EMG) are precious in detecting large-fiber dysfunction, yet unable to diagnose small-fiber neuropathy [2]. More specialized of small-fiber function include sympathetic skin response (SSR), quantitative sensory testing (QST), skin biopsy, pain – related evoked potentials (PREP), etc. Recording pain – related evoked potentials (PREP) are well-designed tool for the evaluation of nociceptive pathways. Several methods have been submitted for selective stimulation of nociceptive Aδ and C fibers by avoiding co-stimulation of non-nociceptive Aβ fibers such as contact heat, laser, intraepidermal electrode and concentric electrode. While the using of contact heat, laser and intraepidermal electrode are either invasive or overprice, the procedure of nociceptive stimulation by concentric electrode is simple, noninvasive, economical and have been studied in healthy subjects and patients with diabetes [3],[8].

In Viet Nam, the appliance of this procedure to evaluate small-fibers function in diabetes has been still limited. *Therefore, we*

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conducted this study to investigate pain – related evoked potentials in healthy subjects as well as patients with diabetes and the relationship between PREP and symptoms in patients with diabetes.

2. METHODS

2.1. Subjects

50 healthy adults (age range: 50 – 71 years, 23 males and 27 females) and 23 patients with diabetes type 2 without neuropathic symptoms (age range: 50 – 73 years, 9 males and 14 females) and 27 patients with diabetes type 2 and neuropathic symptoms (age range: 50 – 74 years, 15 males and 12 females) were included. All patients were diagnosed by using criteria for the diagnosis of diabetes of America Diabetes Association proclaimed in 2018 [1]. Subjects with non-diabetic neuropathy, autoimmune diseases, examined difficulties caused by skin, muscle and vascular injuries were excluded.

2.2. Methods

Study design: cross - sectional descriptive study

Research indexes: In all subjects, pain – related evoked potentials were recorded after stimulus of both upper limbs and lower limbs and Np, Pp latencies, Np-Pp amplitude were analyzed by Neuropack MEB-9400 S1 Series EMG/NCV/EP Measuring System in Electrophysiological laboratory, Hanoi Medical University.

Stimulation: For eliciting PREP, we use a custom built concentric electrode assembly of a central metal cathode and external anode ring (D: 5 – 6 mm) (**Figure 2.1**)

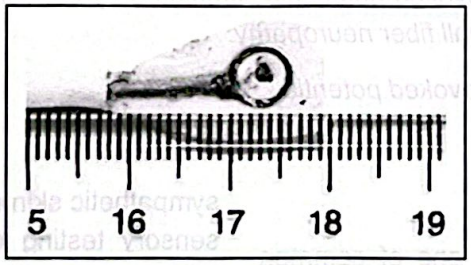

Figure 2.1. Concentric electrode

Stimulus parameters: two electrodes were place on the second phalanges of the second and third digits or the second phalanges of the second and third toes. We applied 10 – 15 double-pulse (intensity: two times of the individual pain threshold, duration: 0.5 ms, double-pulse interval: 5 ms, inter-stimulus interval: 10 s). *Recording:* recording electrode was placed at Cz referred to linked earlobes (A1 – A2) of international 10 – 20 system. *Bandwidth:* 1 Hz – 1 kHz, sweep length: 500 ms.

2.3. Data Analysis

Data was analyzed by using SPSS Statistics 20. The level of significance was set to $p < 0.05$.

2.4. Ethics

Research was performed under the permission of all subjects. Subjects had clear explanation of objectives and research procedures and the right to withdraw from study without explanation. All individual information is kept confidentially.

3. RESULTS

3.1. Morphology of PREP

In 100 subjects, we observed non-producible PREP responses in 10 neuro-symptomatic patients after stimulation. Non-producible PREP responses after stimulation of both upper and lower limbs, lower limbs, right led and left leg were perceived in 2

patients, 3 patients, 4 patients and 1 patient respectively.

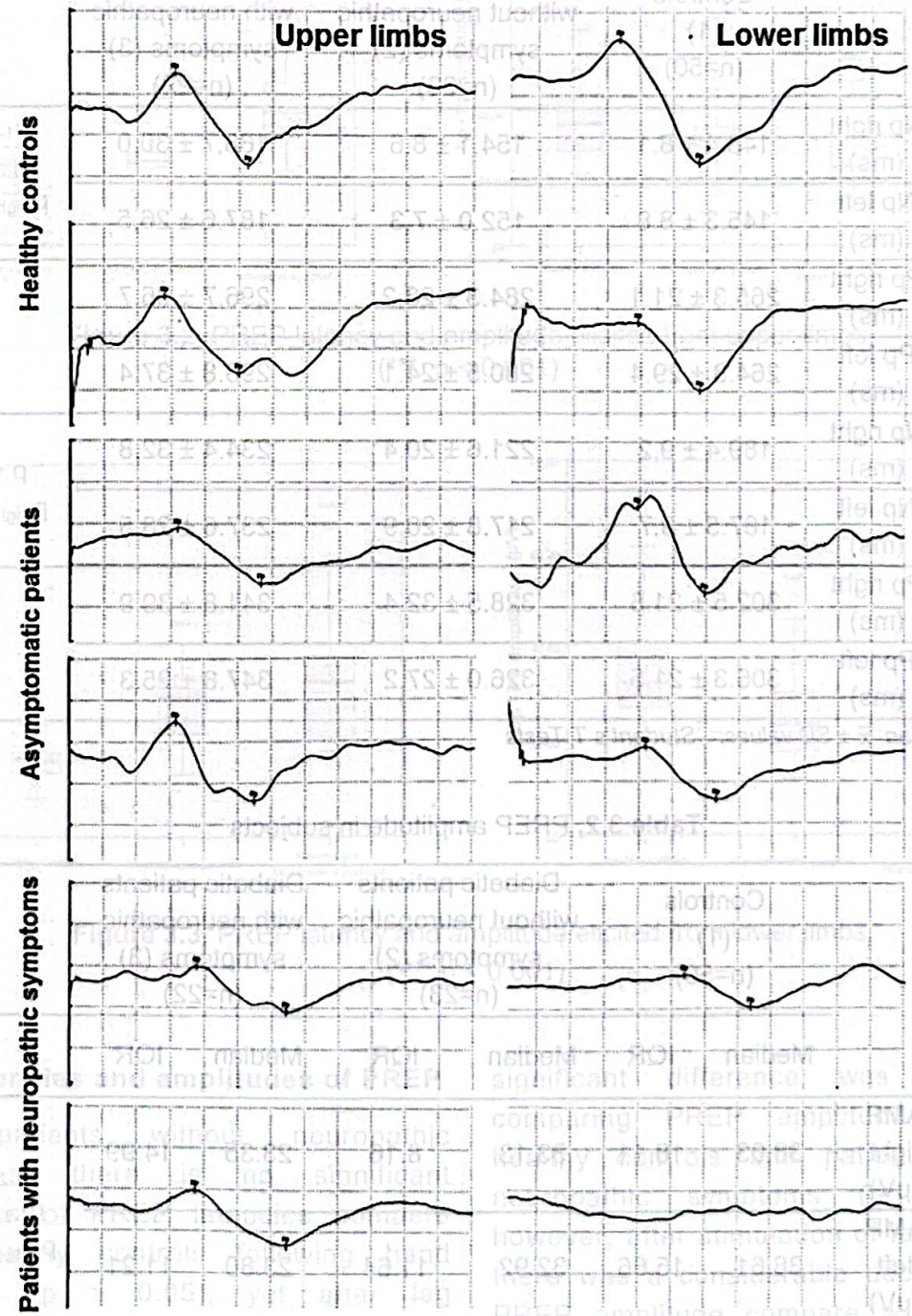

Figure 3.1. Morphology of PREP in subjects

Besides, in three groups, we noticed a negative wave followed by positive wave after stimulation in 73 subjects, a positive wave with two peaks after stimulus of upper or lower limbs in 13 subjects, a unique positive wave after stimulus of lower limbs in 3 subjects. In addition, we noted only one non-symptomatic patient depicted a negative wave with two peaks after stimulation of lower limbs (**Figure 3.1**)

Table 3.1. PREP latencies in subjects

		Controls (1) (n=50)	Diabetic patients without neuropathic symptoms (2) (n=23)	Diabetic patients with neuropathic symptoms (3) (n=22)	
Upper limbs	Np right (ms)	148.4 ± 8.1	154.1 ± 8.6	188,7 ± 30.0	$p_{1-2} > 0.05$ $p_{1-3} < 0.001$ $p_{right-left} > 0.05$
	Np left (ms)	145.3 ± 8.8	152.0 ± 7.3	187.6 ± 26.5	
	Pp right (ms)	265.3 ± 21.1	284.3 ± 26.2	296.7 ± 36.7	
	Pp left (ms)	264.3 ± 29.4	280.5 ± 24.1	296.8 ± 37.4	
Lower limbs	Np right (ms)	189.4 ± 9.2	221.6 ± 20.4	234.4 ± 32.8	$p < 0.001$ $p_{right-left} > 0.05$
	Np left (ms)	187.5 ± 9.7	217.8 ± 20.9	237.6 ± 28.5	
	Pp right (ms)	302.5 ± 21.6	328.5 ± 32.4	341.8 ± 39.9	
	Pp left (ms)	306.3 ± 21.5	326.0 ± 27.2	347.8 ± 25.3	

Data are mean $\bar{x}$ ± SD values; · Student's T Tests

Table 3.2. PREP amplitude in subjects

		Controls (1) (n=50)		Diabetic patients without neuropathic symptoms (2) (n=23)		Diabetic patients with neuropathic symptoms (3) (n=22)		
		Median	IQR	Median	IQR	Median	IQR	
Upper Limbs	AMP right (μV)	38.03	18.11	33.13	8.16	23.35	14.99	$p_{1-2} > 0.05$ $p_{1-3} < 0.001$ $p_{right-left} > 0.05$
	AMP left (μV)	36.61	15.66	32.92	11.64	23.80	11.21	
Lower Limbs	AMP right (μV)	32.93	16.31	23.39	12.62	16.63	10.15	$p < 0.001$ $p_{right-left} > 0.05$
	AMP left (μV)	32.23	15.51	24.24	7.34	16.10	9.2	

IQR: Interquartile Range; · Mann - Whitney test

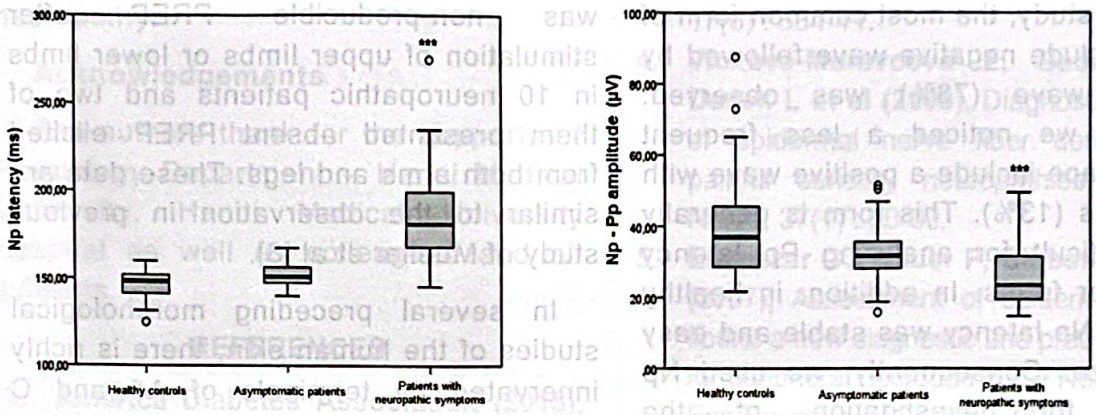

Figure 3.2. PREP latency and amplitude elicited from upper limbs (***: $p < 0.001$)

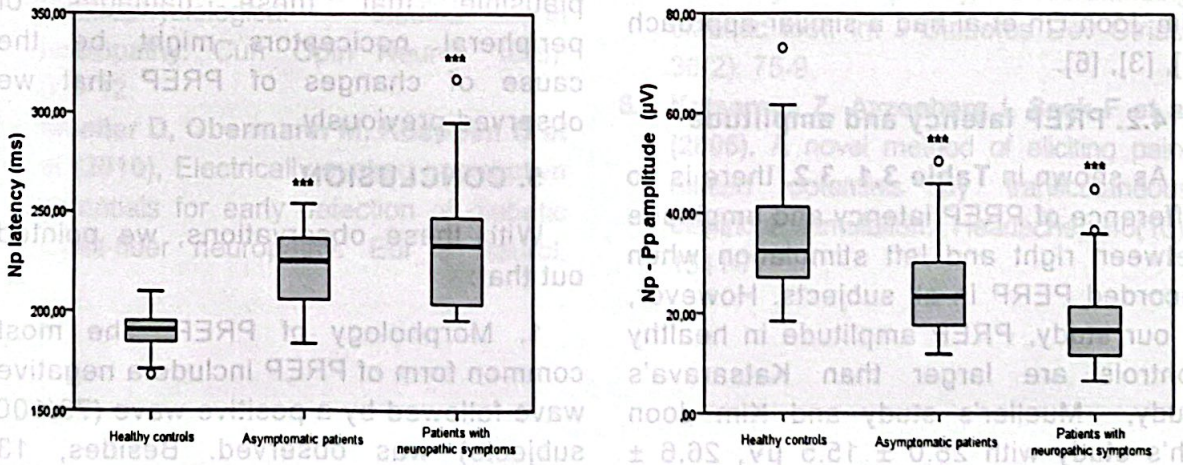

Figure 3.3. PREP latency and amplitude elicited from lower limbs (***: $p < 0.001$)

3.2. Latencies and amplitudes of PREP

In patients without neuropathic symptoms, there is no significant difference of PREP latencies compare with healthy controls following hand stimulus ($p > 0.05$), yet after leg stimulation, considerable increasing of PREP latencies compare with healthy controls was observed ($p < 0.001$). In patients with neuropathic symptoms, compare with healthy controls, we noticed a significant prolongation of PREP latencies elicited from both upper and lower limbs ($p < 0.001$) (Table 3.1). After stimulus of upper limbs, no significant difference was observed comparing PREP amplitude between healthy controls and patients without neuropathic symptoms ($p > 0.05$), however, after stimulation of lower limbs, there was a considerable decreasing of PREP amplitude compare with healthy controls ($p < 0.001$). In patients with neuropathic symptoms, a significant decline of PREP amplitude elicited from both upper and lower limbs compare with healthy controls was noticed ($p < 0.001$) (Table 3.2).

4. DISCUSSION

4.1. PREP morphology

In our study, the most common form of PREP include negative wave followed by positive wave (73%) was observed. Besides, we noticed a less frequent PREP shape include a positive wave with two peaks (13%). This form is generally more difficult for analyzing Pp latency than other forms. In addition, in healthy controls, Np latency was stable and easy to analyze. Consequently, we used Np latency for investigation of the differences between healthy controls and patients with neuropathic symptoms and non-neuropathic symptoms. In previous studies, Katsarava et al, Mueller et al and Kim Joon Oh et al had a similar approach [8], [3], [6].

4.2. PREP latency and amplitude

As shown in **Table 3.1, 3.2**, there is no difference of PREP latency and amplitude between right and left stimulation when recorded PERP in all subjects. However, in our study, PREP amplitude in healthy controls are larger than Katsarava's study, Mueller's study and Kim Joon Oh's study with 28.0 ± 15.5 µV, 26.6 ± 11.5 µV và 19.2 ± 6.7 µV, correspondingly [8], [3], [6]. This difference of race, age of patients as well as healthy controls between our study and previous studies may be considered to be the reasons for the distinction. Besides, a disparity of equipments for recording PREP may contribute to this distinction.

As shown in **Table 3.1, 3.2, Figure 3.1, 3.2**, in patients without neuropathic symptoms, there were significant decreasing of PREP amplitudes and increasing of latencies elicited from lower limbs, while no difference of PREP latency and amplitude was observed ($p > 0.05$). In neuro-symptomatic diabetic patients, there were abnormalities from both upper limbs and lower limbs (prolonged latency and decreased amplitude, $p < 0,001$). In addition, there was non-producible PREP after stimulation of upper limbs or lower limbs in 10 neuropathic patients and two of them presented absent PREP elicited from both arms and legs. These data are similar to the observation in previous study of Mueller et al [3].

In several preceding morphological studies of the human skin, there is richly innervated by terminals of Aδ and C fibers but not of Aβ fibers in the epidermis of the human skin, but there is a decreasing of these fibers in patients with diabetes [4], [5]. Therefore, it seems plausible that these damages of peripheral nociceptors might be the cause of changes of PREP that we observed previously.

5. CONCLUSION

With these observations, we pointed out that:

1. Morphology of PREP: The most common form of PREP include a negative wave followed by a positive wave (73/100 subjects) was observed. Besides, 13 subjects showed a positive wave with two peaks, 3 subjects presented a unique positive wave and only one displayed a negative wave with two peaks.

2. Relationship between PREP and neuropathic symptoms: In patients without neuropathic symptoms, there were significant decreasing of PREP amplitudes and increasing of PREP latencies from lower limbs. In neurosymptomatic diabetic patients, there were abnormalities from both upper limbs and lower limbs.

Suggestions

The method of pain – related evoked potentials elicited by concentric electrode is simple, cheap, easy to apply, noninvasive, reproductive. Hopefully, with our findings, it might contribute to early detection of diabetic small fiber

neuropathy.

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TÓM TẮT

ĐẶC ĐIỂM ĐIỆN THẾ KÍCH THÍCH CẢM GIÁC ĐAU Ở BỆNH NHÂN ĐÁI THÁO ĐƯỜNG TÝP 2

Đỗ Duy Giang, Nguyễn Huy Bình, Lê Đình Tùng

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Tổng quan: *Tổn thương sợi thần kinh nhỏ là một trong những tổn thương thường gặp trong bệnh lý thần kinh ngoại vi do đái tháo đường và cần phát hiện sớm. Vấn đề này được đánh giá thông qua phương pháp ghi điện thế kích cảm giác đau (Pain-related evoked potentials) bằng điện cực kích thích đồng trục bề mặt trong nghiên cứu này.* ***Phương pháp:*** *50 đối tượng khỏe mạnh, 23 bệnh nhân đái tháo đường týp 2 không có biểu hiện triệu chứng thần kinh trên lâm sàng và 27 bệnh nhân có triệu chứng trên 50 tuổi được lựa chọn vào nghiên cứu. Tất cả các đối tượng được ghi điên thế kích thích cảm giác đau chi trên và chi dưới bằng máy điện cơ Neuropack S1 NEB-9400.* ***Kết quả:*** *Dạng sóng chủ yếu ghi nhận được sau kích thích cảm giác đau gồm sóng âm Np và sóng dương Pp (73/100 đối tượng). Ngoài ra, chúng tôi ghi nhận được 3 dạng sóng khác: sóng dương 2 đỉnh (13/100 đối tượng), sóng âm 2 đỉnh (1/100 đối tượng) và chỉ đơn thuần có sóng dương (3/100 đối tượng); ở bệnh nhân đái tháo đường type 2 có biểu hiện triệu chứng thần kinh trên lâm sàng, có kéo dài thời gian tiềm và giảm biên độ các sóng PREP có ý nghĩa sau kích thích đau ở cả chi trên (thời gian tiềm: 188,7 ± 30 ms; biên độ: trung vị 23,35 µV, p < 0,001) và chi dưới (thời gian tiềm: 234,4 ± 32,8 ms; biên độ: trung vị 16,63 µV, p < 0,001), trong khi đó chỉ bất thường sau kích thích đau ở chi dưới (thời gian tiềm: 221,6 ± 20,4 ms; biên độ: trung vị 23,39 µV, p < 0,001) ở nhóm bệnh nhân đái tháo đường không có biểu hiện triệu chứng thần kinh trên lâm sàng.* ***Kết luận:*** *Với kết quả ngiên cứu, chúng tôi cho rằng có thể sử dụng kết quả ghi điện thế kích thích cảm giác đau để phát hiện sớm tổn thương sợi thần kinh nhỏ ngoại vi ở bệnh nhân đái tháo đường týp 2.*

Từ khóa: *điện thế kích thích cảm giác đau, đái tháo đường.*