Assessment of Diabetic Polyneuropathy and Autonomic Neuropathy Using Current Perception Threshold in Korean Patients with Diabetes Mellitus

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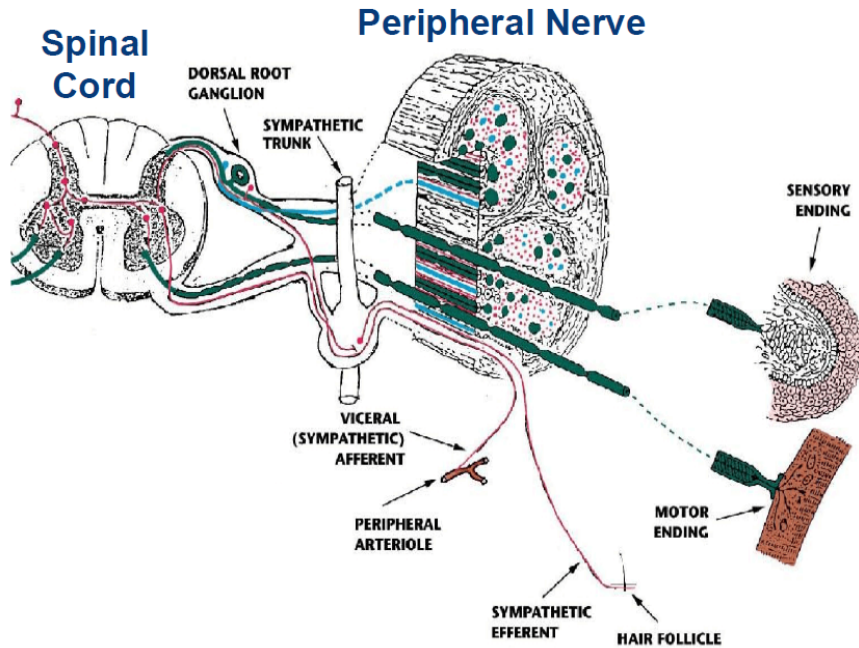[2]Department of Internal Medicine, Boramae Medical Center, Seoul,
[3]Department of Internal Medicine, Seoul National University Bundang Hospital, Sungnam, Korea
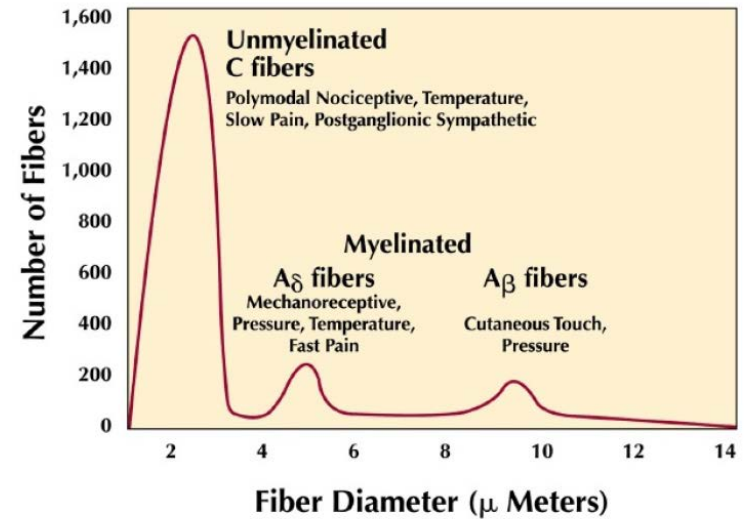
Current Perception Threshold

- Screening for distal polyneuropathy (DPN) is important because up to 50% of patients with diabetic DPN are asymptomatic[1,2].

- Current perception threshold (CPT): minimal strength of alternating current (AC) stimulus that the patient can detect.

- CPT in diabetic patients has been reported to be increased compared to the control subjects.[3,4].

- CPT is able to test different types of nerve fibers by using different electric stimulus frequencies: Aβ, Aδ, and C fibers can be stimulated at 2,000, 250, and 5 Hz, respectively[5].

1. American Diabetes Association. Standards of medical care in diabetes: 2013. Diabetes Care 2013; 2. Boulton AJ, et al., Diabetes Care 2005;28:956-62; 3. Rendell MS et al. *Diabetes Care* 1989; 4. Pitei DL et al., *Diabet Med* 1994; 5. Masson EA et al., *Diabetologia* 1989

Types of Sensory Nerve Fiber

Illustrated nerve fiber types: Aβ (green), Aδ (blue) & C (red) fibers

Aβ fibers	Aδ fibers	C fibers
large myelinated	small myelinated	small unmyelinated
cutaneous touch and pressure sensations	temperature, pressure and fast pain sensations	temperature and slow pain sensations.

Objectives

- We evaluated the usefulness of CPT for the diagnosis of not only distal polyneuropathy (DPN), but also cardiac autonomic neuropathy (CAN) compared to conventional tests in patients with diabetes.

Methods

- Retrospectively reviewed the medical records of patients with diabetes who underwent CPT evaluation from April 2011 to November 2012.

- **Inclusion criteria**
  1) Patients with diabetes aged 30 – 69 years
  2) AST and ALT level <120 IU/L
  3) No active foot disease, such as infection.

- **Exclusion criteria:**
  1) Spine disease or history of cerebrovascular disease,
  2) Other causes of peripheral neuropathy, such as chronic alcoholism
  3) Not performing 10-g monofilament test, or no response to questionnaire for NTSS-6

Evaluation of peripheral neuropathy

- Neuropathy total symptom score-6 (NTSS-6)
  - The subjects with NTSS-6 >6 were defined as symptomatic subjects with neuropathy[1].

- 10-g monofilament test using a 5.07 Semmes-Weinstein monofilament
  - Intact sensation at ≥ 7/10 sites in each foot was considered normal.

- The subjects with NTSS-6 >6 or abnormal 10-g monofilament test results were defined to have DPN.

1. Bastyr EJ 3rd, Price KL, Bril V; MBBQ Study Group. Clin Ther 2005;27:1278-94.
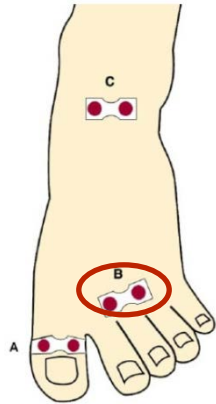
Evaluation of CAN

- Ewing's traditional five simple tests
  - Changes in the R-R with deep breathing, standing, and the Valsalva maneuver
  - Changes in blood pressure in response to standing up and sustained handgrip
  - Subjects with ≥2 abnormalities were considered to have CAN.
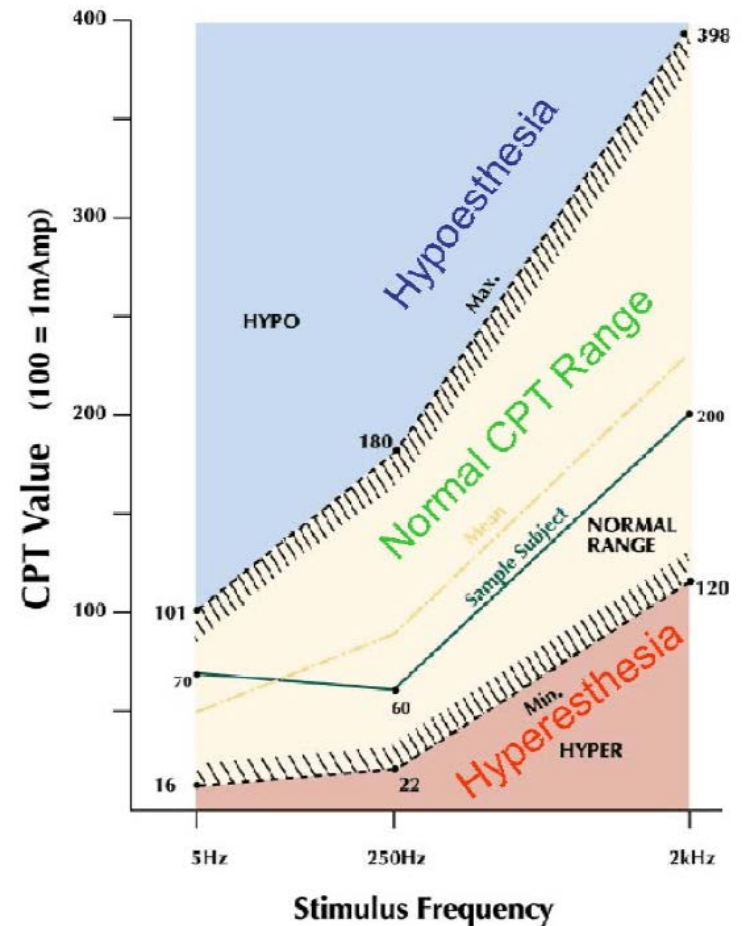
Measurement of CPT using Neurometer
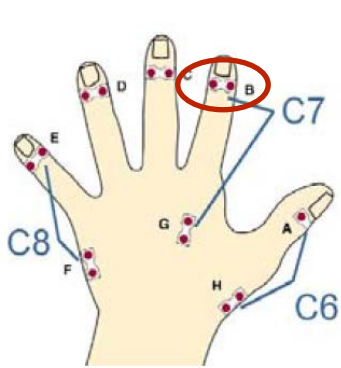
Hand Dermatome Test Sites

Polyneuropathy Test Sites

Finger CPT vs. Frequency
Normal, Hyper & Hypoesthetic Ranges

Clinical Characteristics of the Subjects

- 241 patients with diabetes (124 men and 117 women) were included in our final analysis.
- The prevalence of DPN and CAN were 19.1%.and 18.8%, respectively.

	DPN			CAN		
	Normal	Neuropathy	P^a	Normal	Neuropathy	P^a
N (Men %)	195 (55.4)	46 (34.8)	0.014	104 (50.0)	24 (50.0)	1.000
Age (year)	56 ± 9	61 ± 8	0.137	56 ± 9	57 ± 11	0.567
Duration of diabetes (year)	9 ± 7	15 ± 7	<0.001	7 ± 7	10 ± 9	0.117
BMI (kg/m^2)	25.1 ± 3.8	24.6 ± 3.2	0.558	24.8 ± 3.2	26.3 ± 4.5	0.141
HbA1c (%)	7.9 ± 1.9	8.2 ± 1.7	0.242	7.9 ± 1.9	8.1 ± 1.5	0.623
Triglyceride (mmol/l)	1.6 ± 1.6	1.4 ± 0.7	0.536	1.7 ± 1.9	2.0 ± 1.2	0.177
LDL cholesterol (mmol/l)	2.3 ±0.8	2.2 ± 0.7	0.874	2.4 ± 0.8	2.1 ± 0.6	0.140
DMR, %	147	39		77	18	
No	104 (70.7)	19 (48.7)		65 (84.4)	11 (61.1)	
Mild NPDR	21 (14.3)	5 (12.8)		11 (14.3)	1 (5.6)	
Moderate NPDR	4 (2.7)	3 (7.7)	0.002^b	0	0	<0.001^b
Severe NPDR	4 (2.7)	3 (7.7)		0	0	
PDR	14 (9.5)	9 (23.1)		1 (1.3)	6 (33.3)	
UAE (µg/mg), N (%)	194	46		103	24	
0-29	150 (77.3)	29 (63.0)		85 (82.5)	17 (70.8)	
30-299	29 (14.9)	8 (17.4)	0.015^b	11 (10.7)	4 (16.7)	0.201^b
≥ 300	15 (7.7)	9 (19.6)		7 (6.8)	3 (12.5)	

Nominal variables were presented as frequency (N, %) and continuous variables except CPT values were presented as mean ± standard deviation. CPT value was presented as median (inter-quartile range).
[a]P-value from comparison between subjects with or without neuropathy; [b]P-value from linear-by-linear analysis; [c]P- values from Mann-Whitney test

CPT according to Diabetic Neuropathy
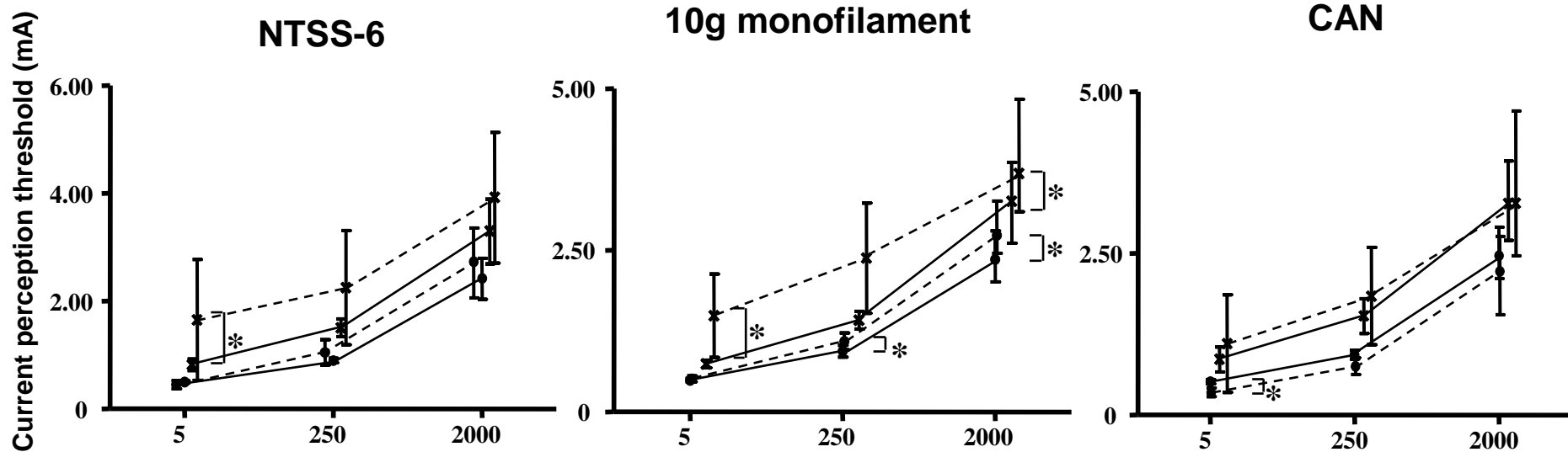
NTSS-6

10g monofilament

CAN

Current perception threshold (mA)

Data are presented as median (interquartile range). Solid and dashed lines represent CPT in the normal and abnormal groups, respectively. Closed circle and X represent CPT at the C7 and L5 levels, respectively. *P < 0.05.

CPT in L5   CPT in C7

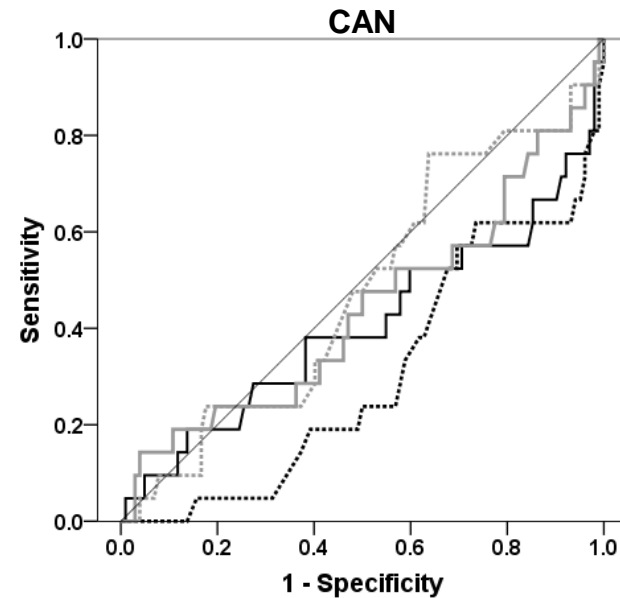# CPT for Predicting Neuropathy

NTSS-6

10g-monofilament test

CAN
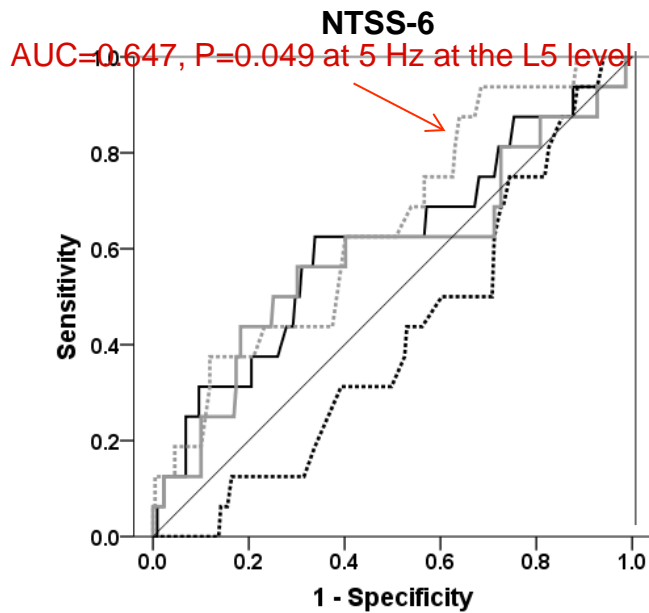
AUC=0.721, *P*<0.001 at 2k Hz at the C7 level

AUC=0.647, P=0.049 at 5 Hz at the L5 level
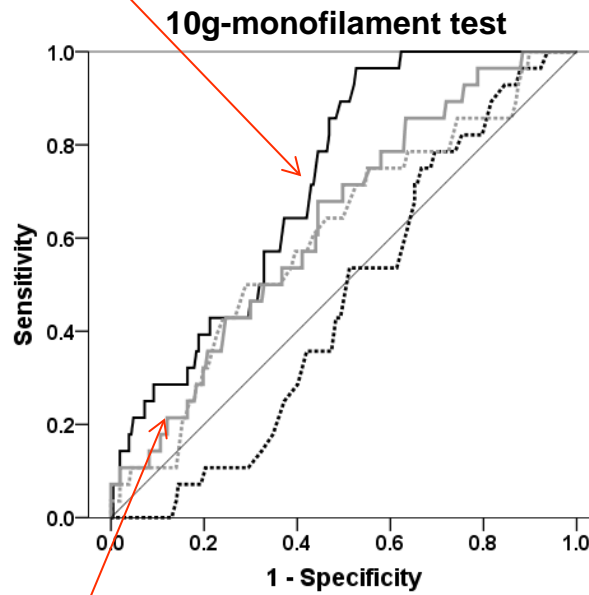
AUC=0.632, P=0.024 at 2k Hz at the L5 level

cpt_c7_2k   cpt_l5_2k
cpt_c7_5_   cpt_l5_5

CPT for Predicting Neuropathy
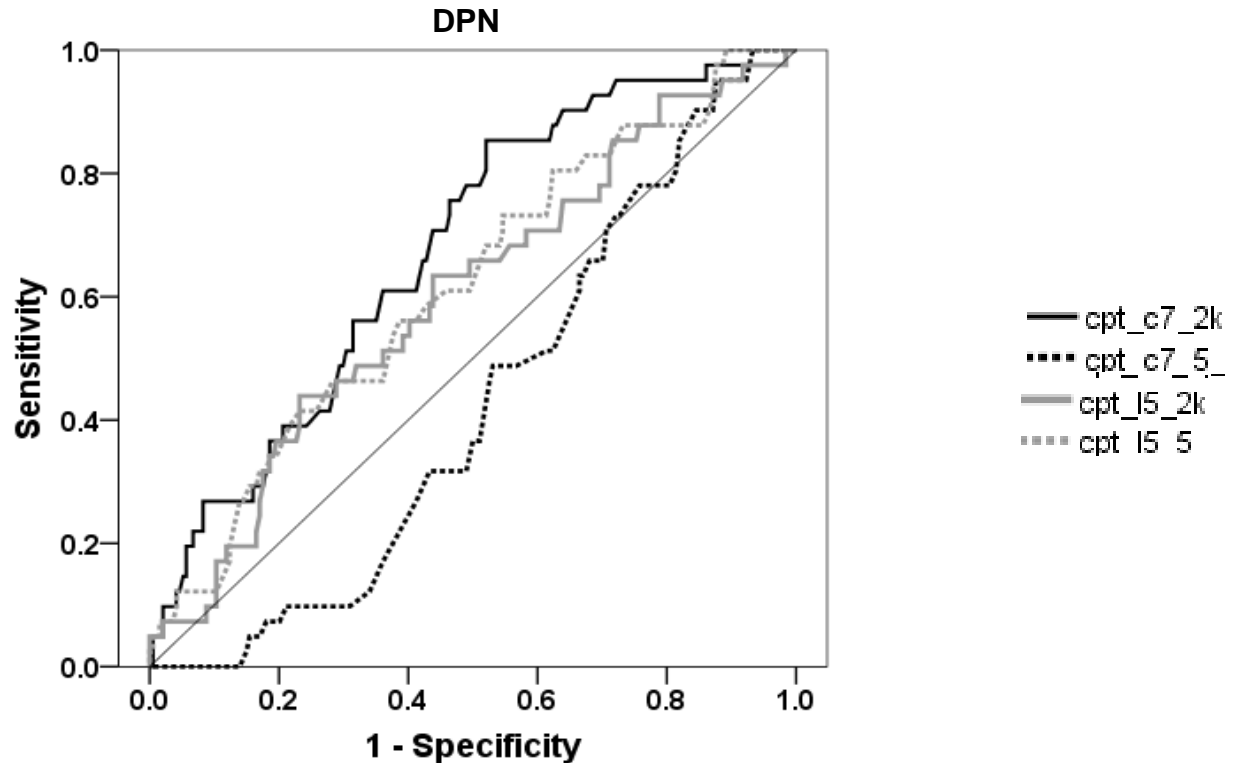
- The ROC analysis showed that CPT measured below could predict the presence of DPN
  - at 2,000 Hz at the C7 levels [AUC 0.676 (*P*<0.001)]
  - at 2,000 Hz at the L5 levels [AUC 0.601 (*P*=0.042)]
  - at 250 Hz at the C7 level [AUC 0.605 (*P*=0.036)]
  - at 5 Hz at the L5 level [AUC 0.607 (*P*=0.019)]

Prevalence of Abnormal CPT

		DPN				CAN			
		No	Yes	P^a	P^b	No	Yes	P^a	P^b
2000 Hz in C7	normal	192 (98.5)	43 (93.5)	0.051	0.019	101 (97.1)	22 (91.7)	0.214	0.716
	hypoesthesia	2 (1.0)	3 (6.5)			3 (2.9)	1 (4.2)		
	hyperesthesia	1 (0.5)	0			0 (0.0)	1 (4.2)		
250 Hz in C7	normal	194 (99.5)	43 (93.5)	0.004	<0.001	102 (98.1)	24 (100.0)	0.494	0.494
	hypoesthesia	0	3 (6.5)			2 (1.9)	0		
	hyperesthesia	1 (0.5)	0			0	0		
5 Hz in C7	normal	186 (95.4)	46 (100.0)	0.138	0.390	103 (99.0)	22 (91.7)	0.031	-
	hypoesthesia	3 (1.5)	0			0	0		
	hyperesthesia	6 (3.1)	0			1 (1.0)	2 (8.3)		
2000 Hz in L5	normal	179 (91.8)	37 (80.4)	0.023	0.003	96 (92.3)	17 (70.8)	0.003	0.006
	hypoesthesia	9 (4.6)	8 (17.4)			5 (4.8)	5 (20.8)		
	hyperesthesia	7 (3.6)	1 (2.2)			3 (2.9)	2 (8.3)		
250 Hz in L5	normal	175 (89.7)	36 (78.3)	0.034	0.007	95 (91.3)	16 (66.7)	0.001	0.002
	hypoesthesia	13 (6.7)	9 (19.6)			6 (5.8)	6 (25.0)		
	hyperesthesia	7 (3.6)	1 (2.2)			3 (2.9)	2 (8.3)		
5 Hz in L5	normal	183 (93.8)	40 (87.0)	0.110	0.001	99 (95.2)	20 (83.3)	0.041	0.184
	hypoesthesia	4 (2.1)	6 (13.0)			3 (2.9)	2 (8.3)		
	hyperesthesia	8 (4.1)	0			2 (1.9)	2 (8.3)		

CPT below or above the reference range obtained from healthy CPT values which was provided by manufacturer was defined as hyperesthesia or hypoesthesia respectively
[a]P- values from chi-square test to compare the frequency of normal vs. (hypoesthesia + hyperesthesia); [b]P-values from chi-square test to compare the frequency of normal vs. hypoesthesia
CAN, cardiovascular autonomic neuropathy

Summary (I)

- CPT was significantly higher in the subjects with DPN compared with the subjects without DPN.

- CPT could predict the presence of significant neuropathic symptoms and light pressure sensation.
  - The neuropathic symptom score and pressure sensation were related to the CPT at 5 and 2,000 Hz, respectively.

- Only 10% to 20% of the subjects with DPN could be classified as having an abnormal CPT.

Summary (II)

- CPT at 5Hz at C7 level were higher in subjects with CAN.

- An abnormal CPT at the L5 level was more frequently found in subjects with CAN.

- The sensitivity to detect CAN was low.
  - Only 29.2%, 33.3%, and 26.7% of subjects with CAN had abnormal CPTs at 2,000, 250, and 5 Hz at the L5 level.

Conclusion

- The CPT at each frequency is significantly associated with neuropathic symptoms or signs corresponding to the nerve fiber stimulated.

- The CPT provides little additional information compared with conventional neuropathic evaluations.

- The current reference range of the CPT should be re-evaluated because of its low sensitivity for detecting diabetic neuropathy.

Thank you for your attention!

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[3]Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, Korea
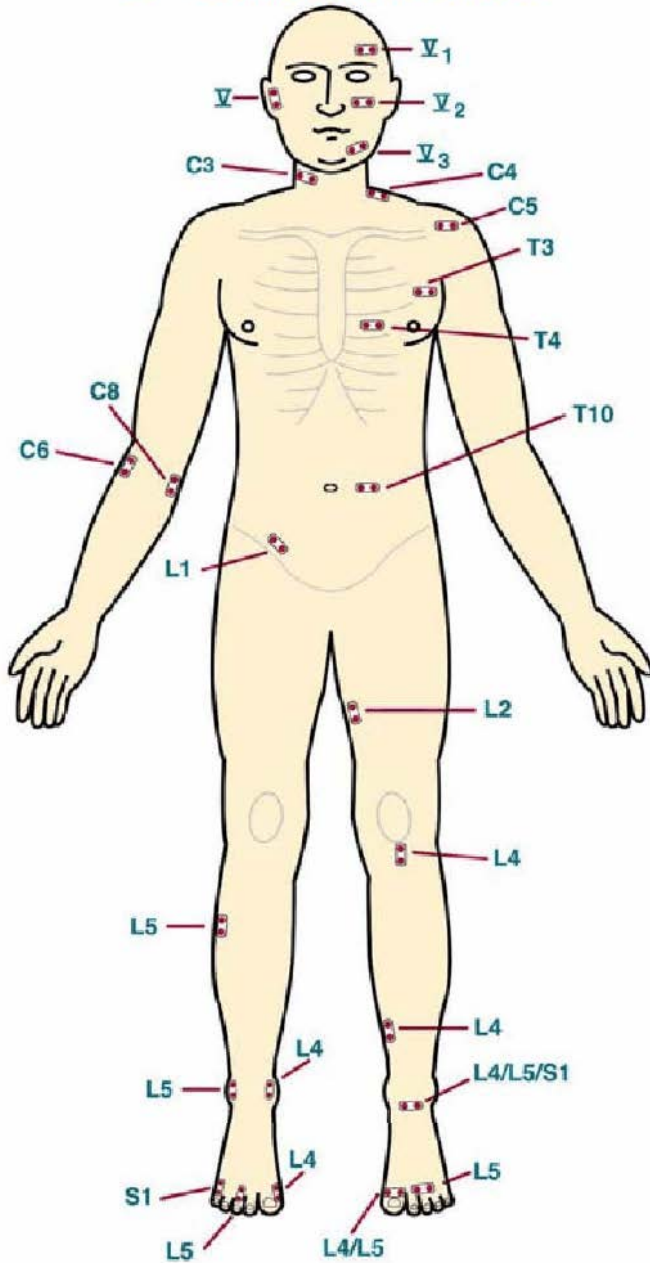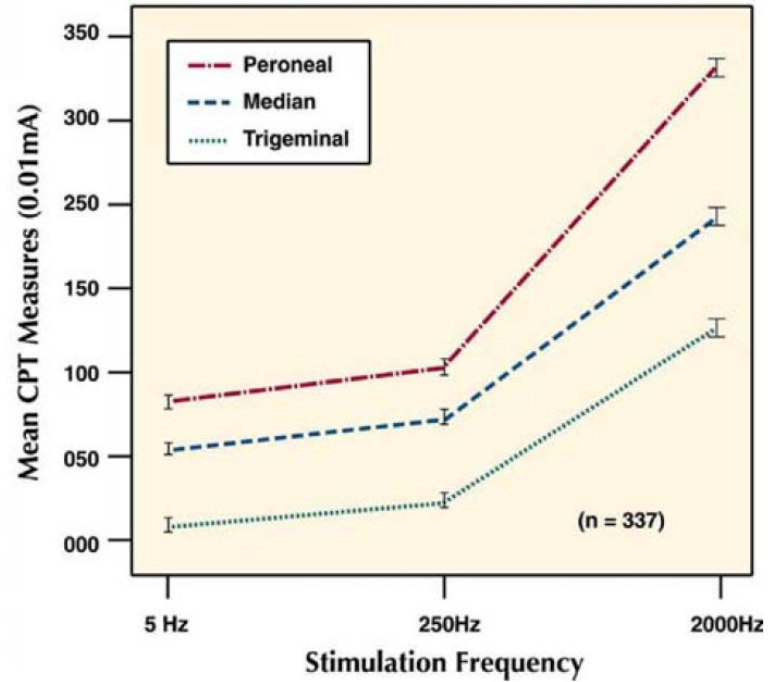
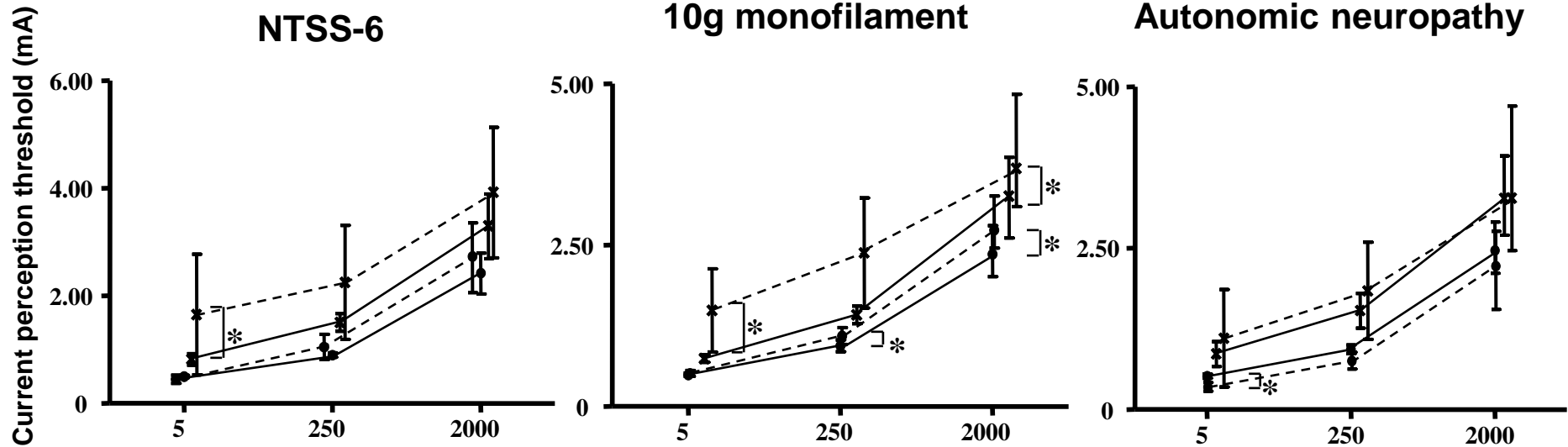# SUPPORTING SLIDES

monofilament
- normal
- abnormal

30-69세
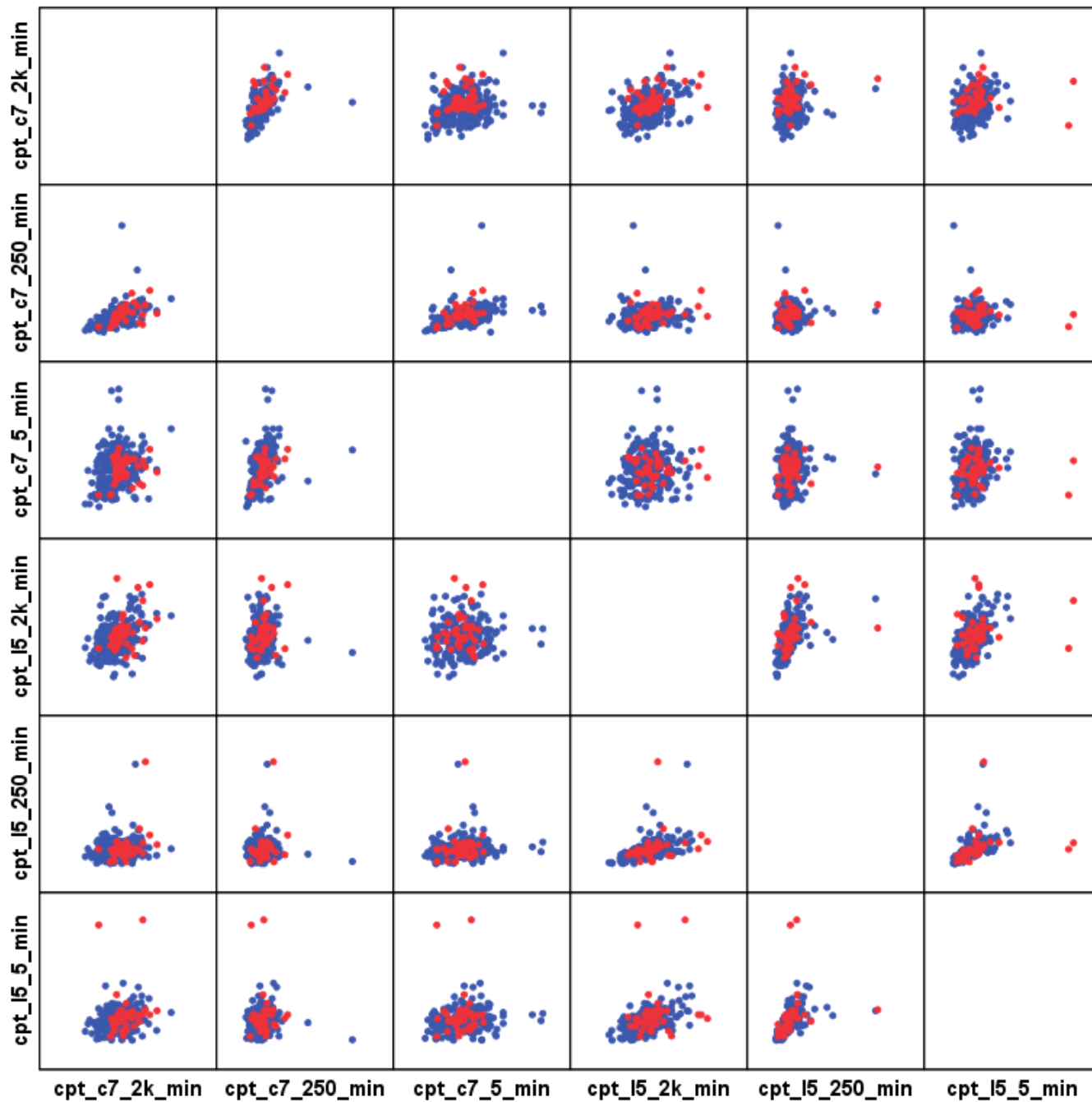
CPT Dermatome Test Sites

CPT Data: Site vs. Frequency

CPT according to Diabetic Neuropathy

NTSS-6

10g monofilament

Autonomic neuropathy

Data are presented as median (interquartile range). Solid and dashed lines represent CPT in the normal and abnormal groups, respectively. Closed circle and X represent CPT at the C7 and L5 levels, respectively. *P < 0.05.

CPT in L5   CPT in C7

	DPN			CAN		
	Normal	Neuropathy	Pa	Normal	Neuropathy	Pa
CPT values						
2000 Hz in C7	236 (77)	269 (84)	0.001	245 (72)	235 (108)	0.090
250 Hz in C7	85.0 (42.5)	101.0 (34.0)	0.030	85.0 (35.3)	85.0 (53.0)	0.077
5 Hz in C7	51.0 (28.5)	47.0 (21.5)	0.087	51.5 (15.0)	45.0 (29.0)	0.002
2000 Hz in L5	322 (121)	352 (123)	0.043	325 (122)	316 (149)	0.380
250 Hz in L5	126.0 (60.5)	137.0 (72.5)	0.047	127.5 (62.3)	124.0 (80.0)	0.255
5 Hz in L5	70.0 (36.0)	78.0 (43.5)	0.005	71.0 (36.8)	70.0 (35.0)	0.805

The CPT are presented as median (interquartile range); aP values from Mann-Whitney test,

Prevalence of Abnormal CPT according to DPN

		NTSS-6 score		10 g-monofilament test		DPN	
		≤6	>6	Normal	Abnormal	No	Yes
2000 Hz in C7	normal	218 (97.8)	17 (94.4)	205 (98.6)	30 (90.9)	192 (98.5)	43 (93.5)[b]
	hypoesthesia	4 (1.8)	1 (5.6)	2 (1.0)	3 (9.1)	2 (1.0)	3 (6.5)
	hyperesthesia	1 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	0
250 Hz in C7	normal	221 (99.1)	16 (88.9)[a,b]	206 (99.0)	31 (93.9)[b]	194 (99.5)	43 (93.5)[a,b]
	hypoesthesia	1 (0.4)	2 (11.1)	1 (0.5)	2 (6.1)	0	3 (6.5)
	hyperesthesia	1 (0.4)	0	1 (0.5)	0 (0.0)	1 (0.5)	0
5 Hz in C7	normal	214 (96.0)	18 (100.0)	199 (95.7)	33 (100.0)	186 (95.4)	46 (100.0)
	hypoesthesia	3 (1.3)	0	3 (1.4)	0	3 (1.5)	0
	hyperesthesia	6 (2.7)	0	6 (2.9)	0	6 (3.1)	0
2000 Hz in L5	normal	203 (91.0)	13 (72.2)[a,b]	191 (91.8)	25 (75.8)[a,b]	179 (91.8)	37 (80.4)[a,b]
	hypoesthesia	13 (5.8)	4 (22.2)	9 (4.3)	8 (24.2)	9 (4.6)	8 (17.4)
	hyperesthesia	7 (3.1)	1 (5.6)	8 (3.8)	0	7 (3.6)	1 (2.2)
250 Hz in L5	normal	199 (89.2)	12 (66.7)[a,b]	185 (88.9)	26 (78.8)[a,b]	175 (89.7)	36 (78.3)[a,b]
	hypoesthesia	16 (7.2)	6 (33.3)	16 (7.7)	6 (18.2)	13 (6.7)	9 (19.6)
	hyperesthesia	8 (3.6)	0	7 (3.4)	1 (3.0)	7 (3.6)	1 (2.2)
5 Hz in L5	normal	209 (93.7)	14 (77.8)[b]	195 (93.8)	28 (84.8)[b]	183 (93.8)	40 (87.0)[b]
	hypoesthesia	6 (2.7)	4 (22.2)	5 (2.4)	5 (15.2)	4 (2.1)	6 (13.0)
	hyperesthesia	8 (3.6)	0	8 (3.8)	0	8 (4.1)	0

CPT below or above the reference range obtained from healthy CPT values which was provided by manufacturer was defined as hyperesthesia or hypoesthesia respectively
[a]P-value<0.05 from chi-square test to compare the frequency of normal vs. (hypoesthesia + hyperesthesia); [b]P-value<0.05 from chi-square test to compare the frequency of normal vs. hypoesthesia
CAN, cardiovascular autonomic neuropathy
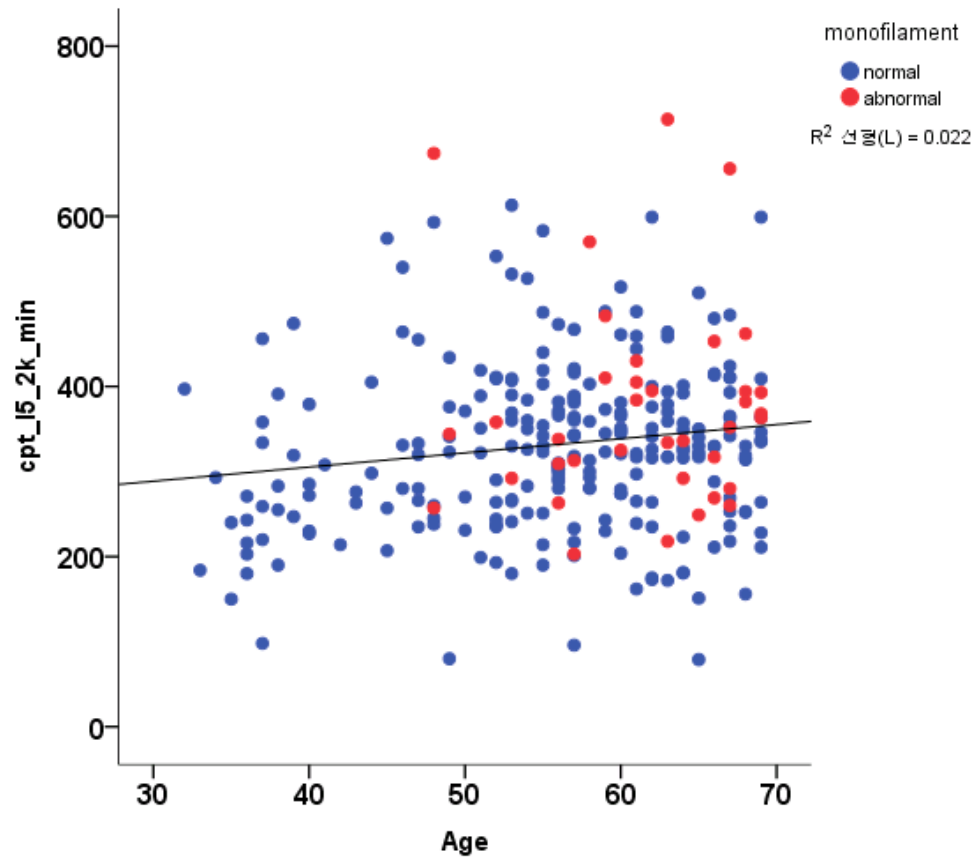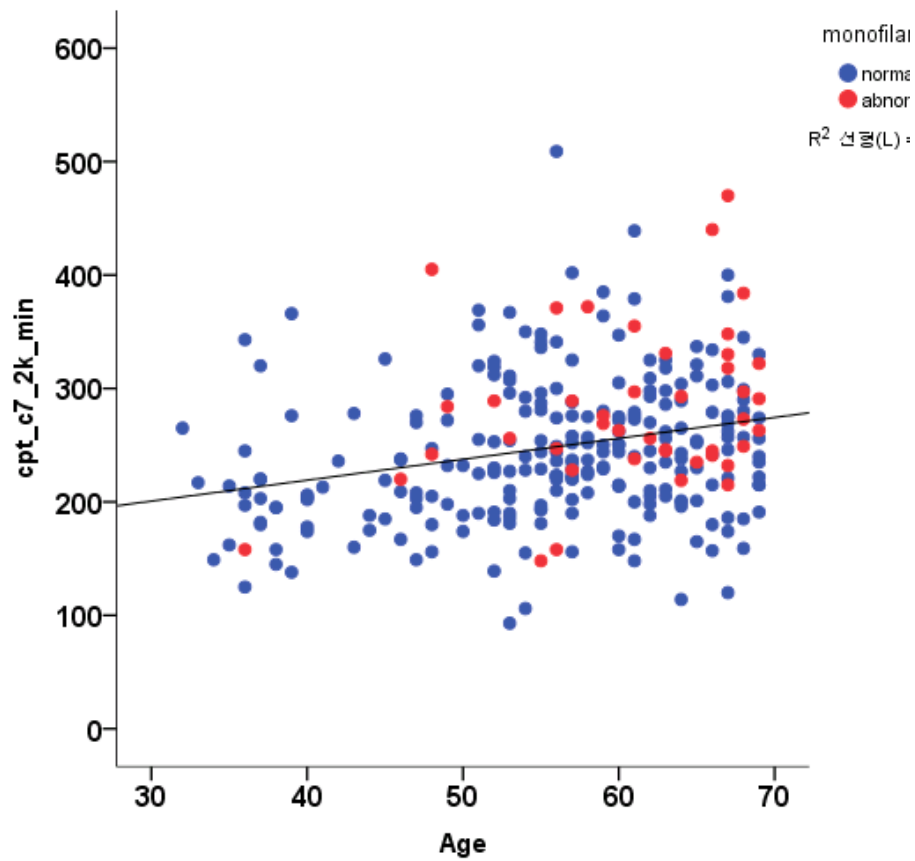
Evaluation of CAN

- Ewing's traditional five simple tests
  - Changes in the R-R with deep breathing, standing, and the Valsalva maneuver
  - Changes in blood pressure in response to standing up and sustained handgrip
  - Subjects with ≥2 abnormalities were considered to have CAN.

- Spectral analysis of heart rate variation (HRV), the standard deviation of all normal R-R intervals (SDNN), and the root-mean square of the difference of successive R-R intervals (rMSSD) were evaluated using DiCAN (Medicore, Seoul, Korea).

Correlation between CPT and the Markers of Autonomic Neuropathy

	SDNN		rMSSD		TP		LF		HF	
	ρ^a	*P*-value	ρ^a	*P*-value	ρ^a	*P*-value	ρ^a	*P*-value	ρ^a	*P*-value
2000 Hz in C7	−0.205	0.010	−0.040	0.623	−0.185	0.022	−0.267	0.001	−0.118	0.146
250 Hz in C7	−0.106	0.190	0.039	0.629	−0.078	0.338	−0.120	0.138	0.003	0.975
5 Hz in C7	−0.051	0.528	−0.017	0.832	−0.001	0.987	0.057	0.486	0.027	0.737
2000 Hz in L5	−0.099	0.228	−0.010	0.907	−0.109	0.185	−0.161	0.050	−0.070	0.394
250 Hz in L5	− 0.116	0.156	−0.127	0.118	−0.133	0.104	−0.142	0.083	−0.201	0.014
5 Hz in L5	−0.175	0.031	−0.132	0.104	−0.164	0.043	−0.161	0.047	−0.207	0.011

[a]Spearman's Rank correlation test
SDNN, standard deviation of all normal R-R intervals; rMSSD, root–mean square of the difference of successive R-R intervals; TP, total power from spectral analysis of heart rate variability; LF, power of low frequency from spectral analysis ; HF, power of high frequency from spectral analysis

Small Fiber Neuropathy

- The small myelinated, **Aδ fibers** and unmyelinated **C fibers** are responsible for conducting protective sensations that guard against serious injury.
  - Clinical complications resulting from C fiber polyneuropathy include foot ulceration, gangrene, cardiac and other types of autonomic dysfunction.

- *"Painless Neuropathy"*
  - selective loss of smaller fiber protective sensation.
  - intact large fiber touch sensation
  - may be unaware of the neuropathy, greatly increasing the risk of serious injury.

Loss of Large Myelinated Fibers

- Disturbance of light tough sensation, sensibility to pressure and vibration, and joint position sense

- Distal weakness
  - Late event in the natural history of diabetic polyneuropathy
  - Associated with severe sensory loss

Predominantly motor neuropathy is not a feature of distal neuropathy in patients with T2DM.

Progressive Neuropathy

Healthy
(normal electrical sensory threshold)

Hyperesthesia
(lowered electrical sensory threshold)

Hypoesthesia
(elevated electrical sensory threshold)

Motor Nerve Damage
(weakness)

Anesthesia
(absent sensory response)