遠離中風走

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主辦單位：台灣腦中風關懷協會、澄清綜合醫院、台灣腦中風醫學會

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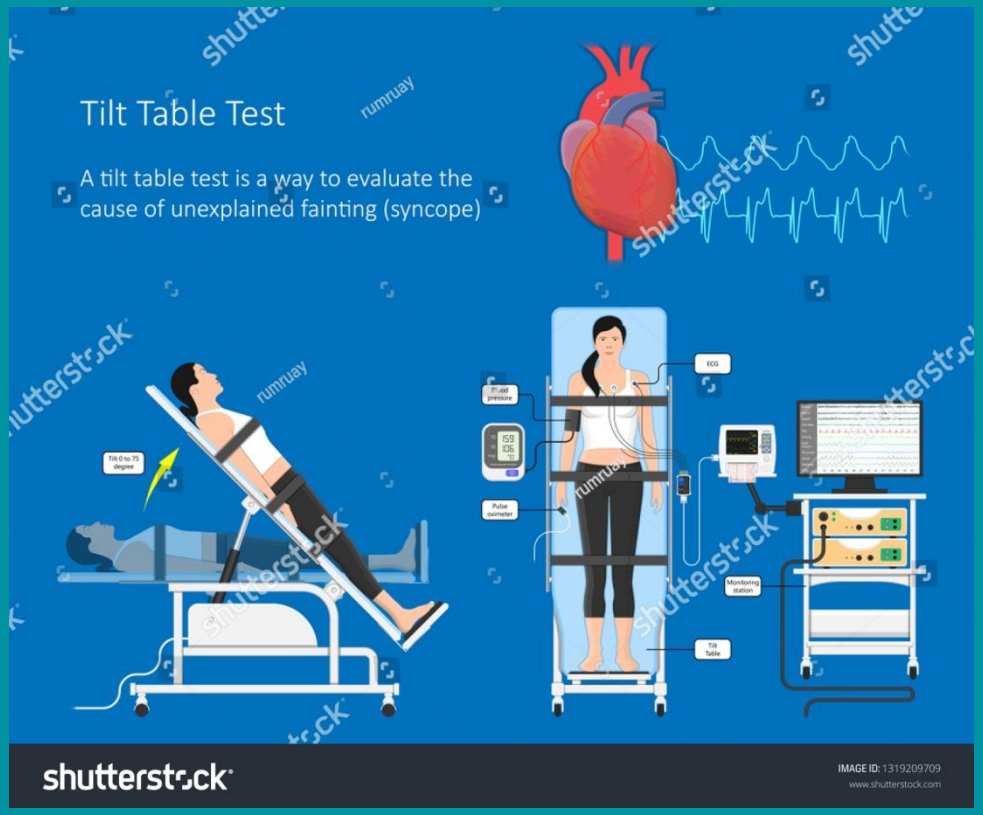
The Late Onset POTS in Prodromal Parkinson's disease



Shoou-Jeng Yeh 葉守正

台灣腦中風學會第12屆理事長
台灣腦中風關懷協會 理事長
台灣神經學會自律神經/暈眩學組召集人
澄清醫院 神經內科主任

The Whole Spectrum of Postural Orthostatic Tachycardia Syndrome (POTS)

POTS From Tilting Test and Clinical Point of View

Standing Up To POTS®

Postural Orthostatic Tachycardia Syndrome Facts

- Approximately 500,000 to 3,000,000 Americans suffer from POTS.
- 1% of US teens likely have POTS, and it is 5x more common in women than men.
- People of all ages can develop POTS, but it is most common in women ages 15-50.
- Current research indicates that POTS may be an autoimmune condition.
- 25% of POTS patients are too sick to work or attend school.

Postural Orthostatic Tachycardia Syndrome (POTS)

- **△HR ≥ 30 or HR ≥ 110 within 10 min tilting**
- **No orthostatic hypotension**
- **Experience lightheadedness, dizziness and instability while standing up and relieved by sitting or lying down**

What are the symptoms of POTS?

POTS usually suffer from two or more of the many symptoms listed below.
Not all patients with POTS have all these symptoms.

- Dizziness/lightheadedness
- Earthquake-like feeling
- Fainting/syncope
- Blurred vision
- Exhaustion/fatigue
- Chest pain
- Abdominal pain and bloating
- Trouble focusing (brain fog)
- Nervous, jittery feeling
- Insomnia
- Shakiness/tremors
- Discoloration of feet and hands
- Exercise intolerance

Clinical overlap (Similar Conditions)

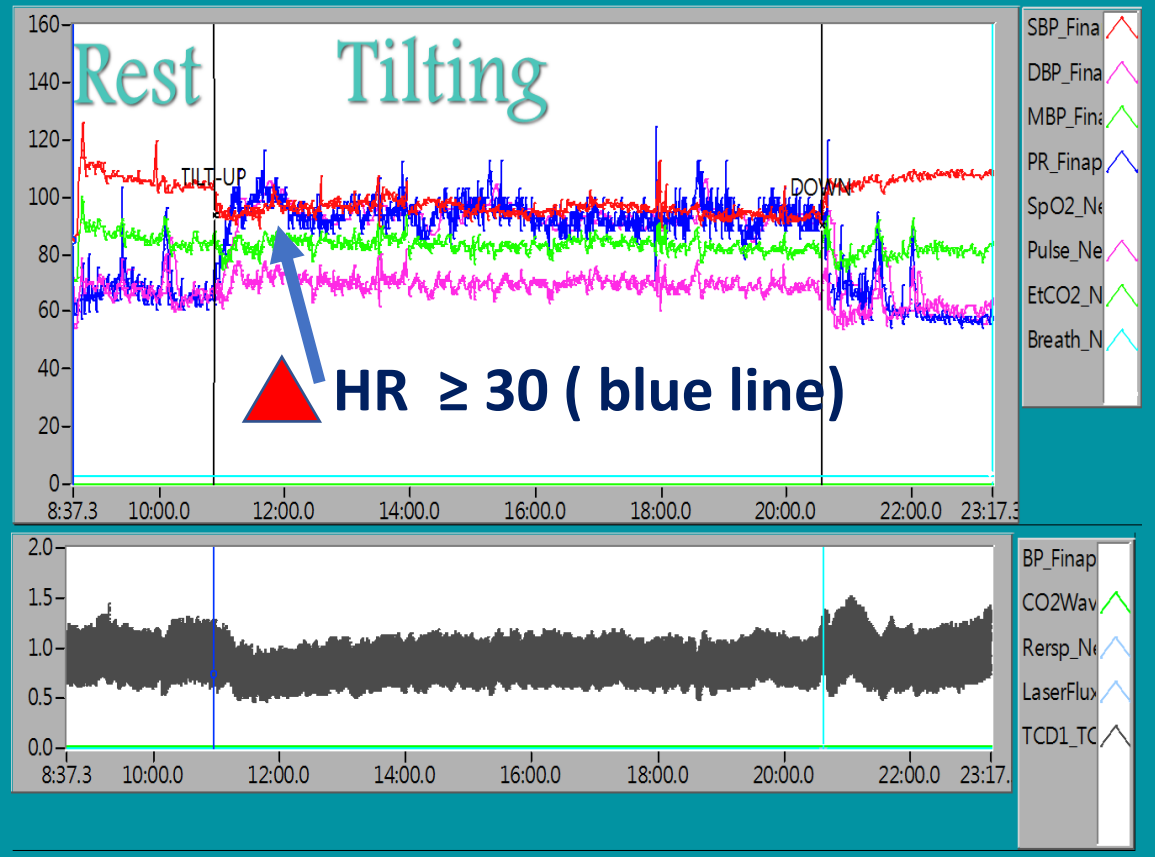
- Mitral valve prolapse
- Hyperadrenergic syndrome
- Inappropriate sinus tachycardia (IST)
- Anxiety
- Hyperventilation syndrome

POTS Comobid Disease

- Low Pressure Headache
- Thalassemia
- Early Diabetic Autonomic Neuropathy

Case Demo :24 y/o Female with Syncope

- Syncope on Mar 4, 2021
- Fainting spell frequently
- Syncope 5 times within 2 yrs
- Episodes of palpitation & HV
- Insomnia--O(+), D(+), M(+) for 1-2 yrs.
- No anemia, Hb : 13.50 g/Dl



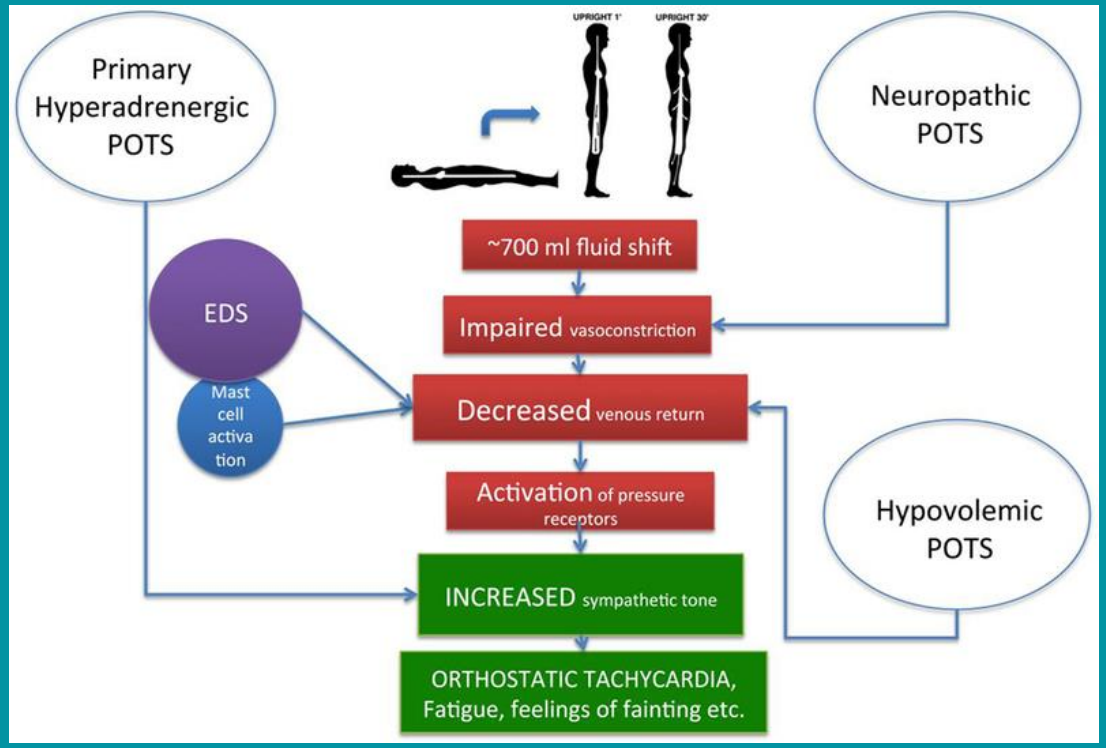
6092780 張O菱 110/03/10

What is POTS?
There are various forms of POTS

- **I. Neuropathic POTS**: Peripheral denervation leads to poor blood vessel muscles, especially in the legs and core body.

- **II. Hyperadrenergic POTS**: Overactivity of the sympathetic system.

- **III. Low blood volume POTS**: Reduced blood volume can lead to POTS. .



Idiopathic postural orthostatic tachycardia syndrome

- NEUROLOGY 1993;43:132
- Ronald Schondorf and Phillip A. Low
- **An attenuated form of acute pandysautonomia? 40-50%?**

Idiopathic postural orthostatic tachycardia syndrome

Mayo Autonomic Reflex Laboratory:

- **These patients were usually women who experienced an acute onset of persistent lightheadedness and fatigue or gastrointestinal dysmotility.**
- **A viral illness may have preceded the onset of symptoms.**
- **Signs and symptoms of a small-fiber sensory neuropathy were present.**
- **Laboratory evaluation of autonomic function revealed increased Valsalva ratio, marked decrease in phase II of the Valsalva maneuver with normal phase IV overshoot,**
  1. **normal forced respiratory sinus arrhythmia.**
  2. **Abnormal quantitative sudomotor axon reflex test (QSART) and thermoregulatory sweat test (TST)**
  3. **An excessive orthostatic increase of catecholamines were found in some patients.**

We conclude that in many instances POTS may be a manifestation of a mild form of acute autonomic neuropathy.

QSART vs. SSR study

Skin Sympathetic Response in Postural Tachycardia Syndrome

Shoou-Jeng Yeh, Jon-Son Kuo[1]

Department of Neurology, Cheng-Ching Hospital,
[1]Department of Education and Research, Taichung Veterans General Hospital,
Taichung, Taiwan

Abstract - Postural tachycardia syndrome (POTS) is characterized by the development of orthostatic symptoms associated with a heart rate (HR) increments of 30 beat-per-minute (bpm) or greater without orthostatic hypotension. We report the skin sympathetic responses (SSR) in Chinese people with POTS. We enrolled 16 patients with POTS (five men and 11 women, age range, 21-57 years) and 16 healthy volunteers as controls (five men and 11 women, age range, 19-59 years) and performed SSR on both palms and soles simultaneously using electric stimulation at the wrist median nerve of each participant. The latency of SSR was more consistent among the healthy volunteers and patients, but marked variations in amplitude were noted between the two groups. Four out of the 16 patients displayed absence of SSR in soles and two in palms. The amplitude of SSR in soles was reduced in patients with POTS ($P < 0.005$). There were significant differences in SSR latencies between the healthy volunteers and patients with POTS ($P < 0.05$, in palms and $P < 0.005$, in soles, respectively). We concluded that sympathetic sudomotor fibers are impaired in some Chinese patients with POTS and SSR may be a simple way to identify many patients with POTS with autonomic neuropathy.

4/16= 25%

Key Words: Orthostatic intolerance, Sympathetic skin response

Acta Neurol Taiwan 1999;8:166-169

Table 1. *Age and sex distribution of the control group and patients with POTS*

	Control	POTS
Number	16	16
Age (years)	31.8 ± 11	33.4 ± 9.3
Sex (M:F)	5 : 11	5 : 11

Table 2. *SSR Data from controls and POTS*

	Controls (n=16)	POTS (n=16)	*P value*
Latency (seconds)			
palms	1.48 ± 0.19	1.68 ± 0.22(n=14)	0.0320
soles	1.97 ± 0.29	2.32 ± 0.21(n=12)	0.0013
Amplitudes (mV)			
palms	2.93 ± 1.51	2.09 ± 1.09(n=16)	0.1907
soles	1.59 ± 0.99	0.51 ± 0.41(n=16)	0.0008

n: number of subjects.

The Acute or Subacute Autonomic Neuropathies

- ***Autoimmune autonomic neuropathy (pandysautonomic)***
- Paraneoplastic autonomic neuropathy
- Acute cholinergic neuropathy
- Guillain –Barre syndrome with autonomic failure
- Botulism
- Porphyria
- Drug induced acute autonomic neuropathies

  cisplatin,Vincristine,Vacor,Amiodarone,Perhexiteme,Taxol
- Toxic acute autonomic neuropathies?

  Heavy metals,organic solvents,Acrylamide,Hexacarbons

Autoimmune Autonomic Neuropathy (AAN)

- Suarez et al 1994
- N=27;Mean age 45years
- Acute to subacute onset
- Generalized autonomic failure
- Post-infection in 50%
- Somatic Sx not uncommon, but EMG normal

- AAN runs the full spectrum of mode of onset and course from subacute to chronic
- High antibody levels are closely associated with OH +, cholinergic neuropathy of eyes , skin, bladder and GUT
- Chronic AAN can be associated with:
  -High autoantibody levels
  -Chronic progressive course
  -Chronic remittent course
  -PAF-like pattern

Ganglionic Antibody

AUTOANTIBODIES TO GANGLIONIC ACETYLCHOLINE RECEPTORS IN AUTOIMMUNE AUTONOMIC NEUROPATHIES
Steven Vermio,M.D,PhD;PHILLP A . LOW,MD;JON D,STEWART,MB,B.S.
GIANRICO FARRUGIA, MD;AND VANOA,MD,PhD

- Vernino et al N Engl J Med 2000;343:847-855
- Antibody to neuronal nicotinic acetylcholine receptors of autonomic ganglia(A3)
- Immunoprecipitation assay, ^{125}I-epibatidine and solubilized ganglionic receptor used to detect binding and blocking antibodies

Disorders of the Autonomic Nervous System

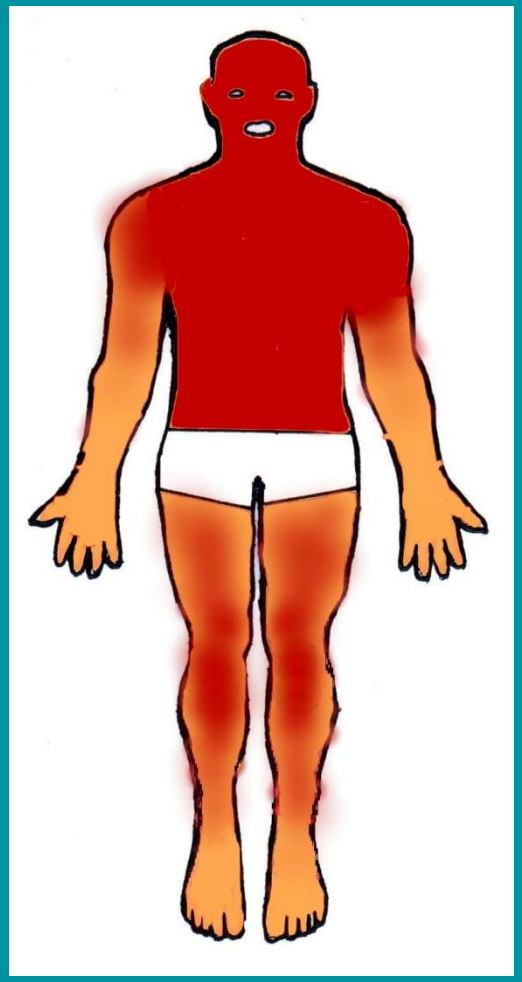
Joseph Jankovic MD, in Bradley and Daroff's Neurology in Clinical Practice, 2022

Autoimmune Autonomic Ganglionopathy

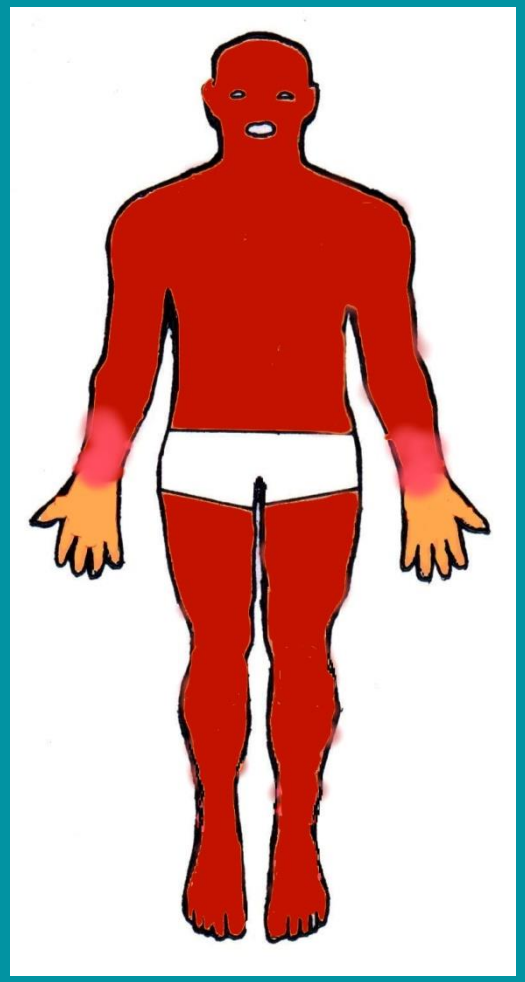
- ***Also known as autoimmune autonomic neuropathy (AAN) and acute pandysautonomia (Vernino et al., 2000), autoimmune autonomic ganglionopathy typically strikes a previously healthy individual.*** Severe generalized sympathetic and parasympathetic autonomic failure unfolds over a few days to a few weeks. Orthostatic hypotension, fixed heart rate, anhidrosis, dry mouth, dry eyes, sexual dysfunction, constipation, and impaired pupillary function are present (Vernino et al., 2000). Anorexia, early satiety, postprandial abdominal pain and vomiting, constipation, or diarrhea may also be present. The spectrum and severity of dysautonomia is quite variable, however. Motor and sensory nerve abnormalities are typically absent. The most convincing evidence of an autoimmune pathogenesis is the demonstration of ganglionic nicotinic acetylcholine receptor (AChR) antibodies in high titers in a large proportion of these patients, the correlation of antibody level with dysautonomia severity, and the response of this disorder to intravenous globulin and plasma exchange (Vernino, 2005). Animal studies have demonstrated passive transfer of the disorder with infusion of patient serum. Antibody-mediated impairment of synaptic transmission occurs in autonomic ganglia (Vernino et al., 2000).
- Like other autoimmune disorders, autoimmune autonomic ganglionopathy may occur in a postinfectious or postsurgical setting, in the context of other autoimmune disorders such as autoimmune thyroiditis, with pernicious anemia or type 1 diabetes, as a result of a monoclonal antibody, or as a paraneoplastic disorder. Typical malignancies include small-cell carcinoma of the lung, breast cancer, lymphoma, and a scattering of other cancers. An elevated level of serum ganglionic AChR antibody is specific for the diagnosis, but its absence does not rule it out, since not all antibodies are detectable by current methodology. Particularly suggestive of this disorder are the spectrum of neurogenic bladder, impaired pupillary function, gastroparesis, dry eyes, and dry mouth.
- ***Treatment includes plasma exchange or intravenous immunoglobulin (Schroeder et al., 2005). Partial but incomplete improvement over time is typical. Only a third of patients experience major functional improvement of autonomic deficits.*** Some patients with a more insidious and progressive form (rather than the typical subacute monophasic presentation) may be clinically indistinguishable from PAF. It is likely other antibodies play a role in the production of autonomic disorders, such as antibodies to muscarinic cholinergic receptors, α-adrenergic receptors, and β-adrenergic receptors. This would typically involve dysfunction of a very selective type, involving either pure adrenergic or pure cholinergic failure, or isolated gastrointestinal dysmotility.

Case 1. 陳0華(M,33) 5351797:
acute onset of hypohydrosis with heat intolerance during excercise

TST

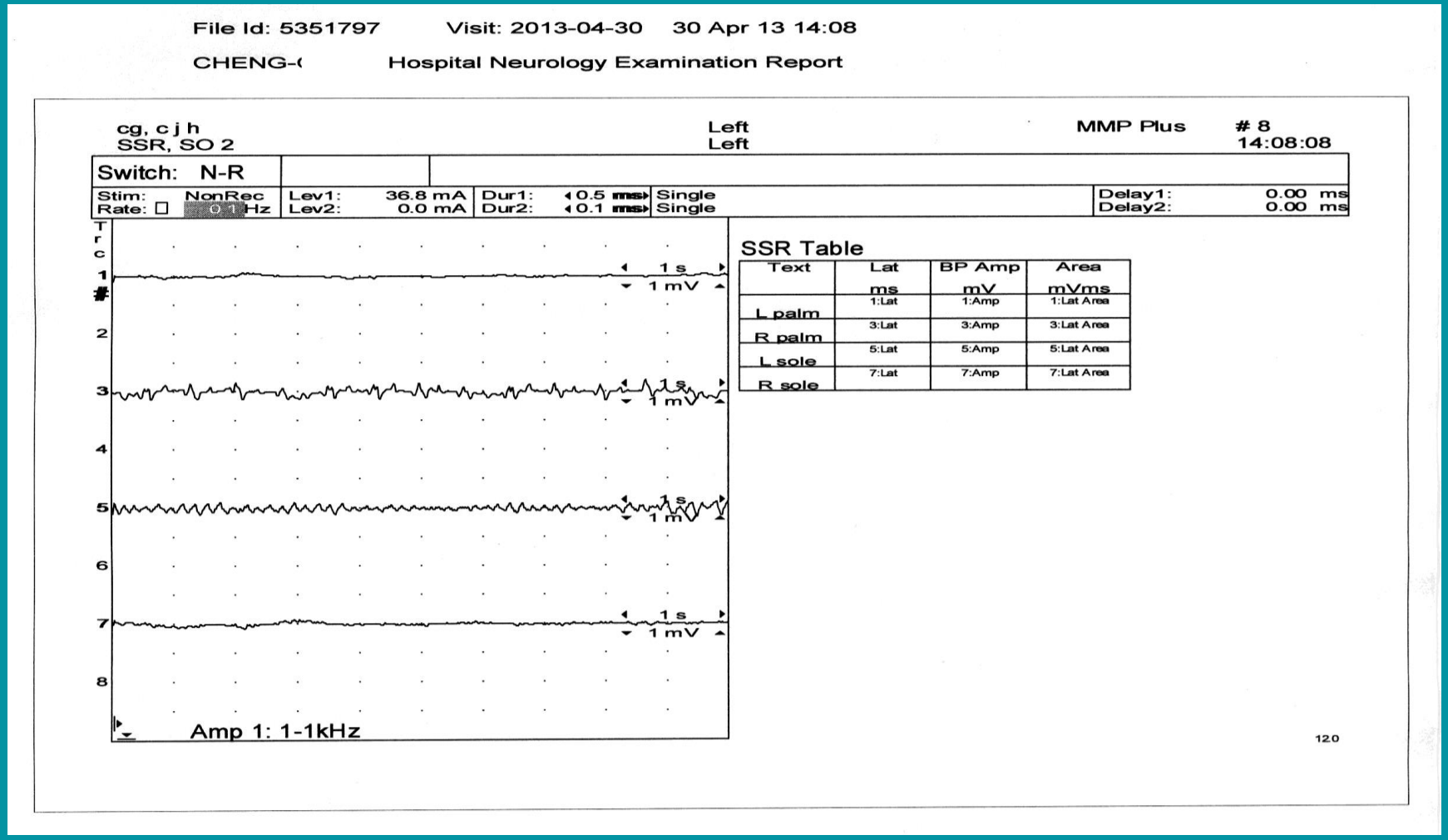


2013/04/30



2013/08/13

Sympathetic Skin Response



File Id: 5351797 Visit: 2013-04-30 30 Apr 13 14:08

CHENG-(Hospital Neurology Examination Report

cg, c j h
SSR, SO 2

Left
Left

MMP Plus # 8
14:08:08

Switch: N-R

Stim: NonRec
Rate: 0.1 Hz

Lev1: 36.8 mA
Lev2: 0.0 mA

Dur1: 0.5 ms
Dur2: 0.1 ms

Single
Single

Delay1: 0.00 ms
Delay2: 0.00 ms

Trc
1
#
2
3
4
5
6
7
8

1 s
1 mV

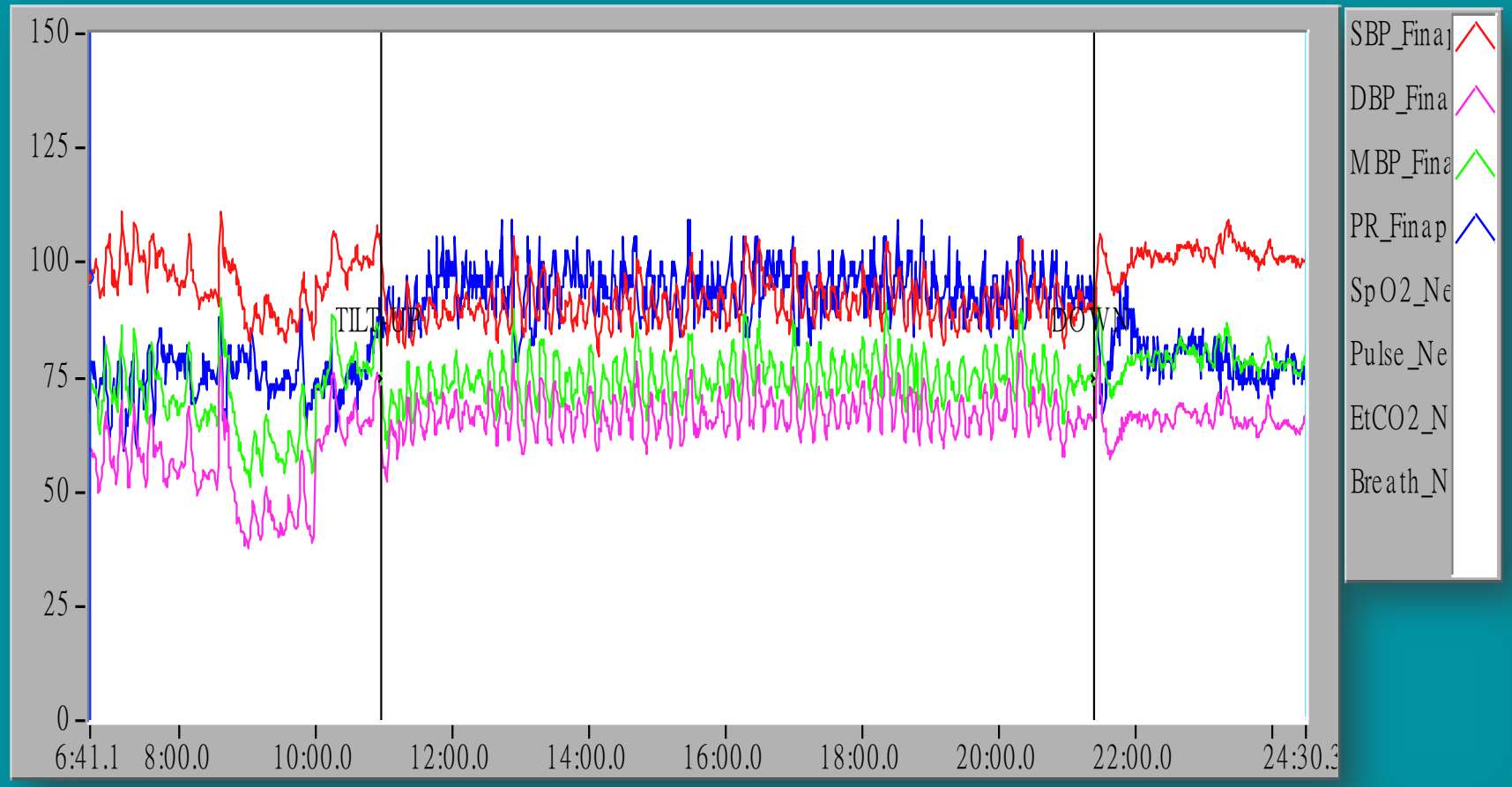
Amp 1: 1-1kHz

SSR Table

Text	Lat ms	BP Amp mV	Area mVms
L palm	1:Lat	1:Amp	1:Lat Area
R palm	3:Lat	3:Amp	3:Lat Area
L sole	5:Lat	5:Amp	5:Lat Area
R sole	7:Lat	7:Amp	7:Lat Area

120

Tilting: POTS Pattern

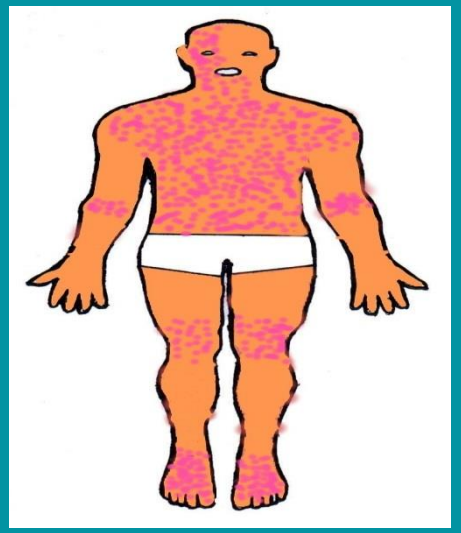


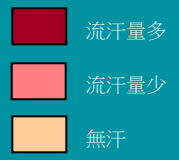
CASE 2: 48 y/s 男性

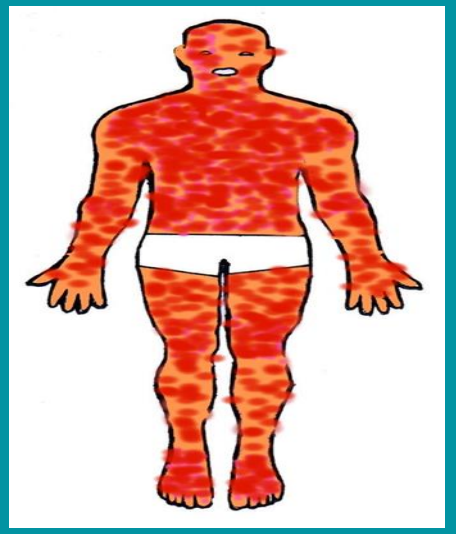
檢查日期：96/05/24

治療前

治療後







Acute to Subacute Anhydrosis or Hypohydrosis in CCH, Skin Biopsy and MTP Treatment Response

---Immune Mediated Small Fiber Neuropathy?

男性為主

	NL	MILD	MARKED	TOTAL
No (M/F)	10 (8/2)	6 (6/0)	9 (8/1)	**25 (22/3)**
Age	32.3	33.4	31.1	**32.2**
POTS	5 (50%)	2 (33.3%)	4 (44.4%)	**11 (44%)**
Prognosis: Rx to MTP	8 (80%)	4 (60%)*	6 (66.7%)	**18/23 (78.2%)**

* 有兩位未接受治療,一位是 TST 正常,一位是DM(首次確診)

有5個病人有送抗體

張X安
Anti-GM1 陽性

李X龍
Anti-Amphiphsyin 陽性

其他三位皆陰性

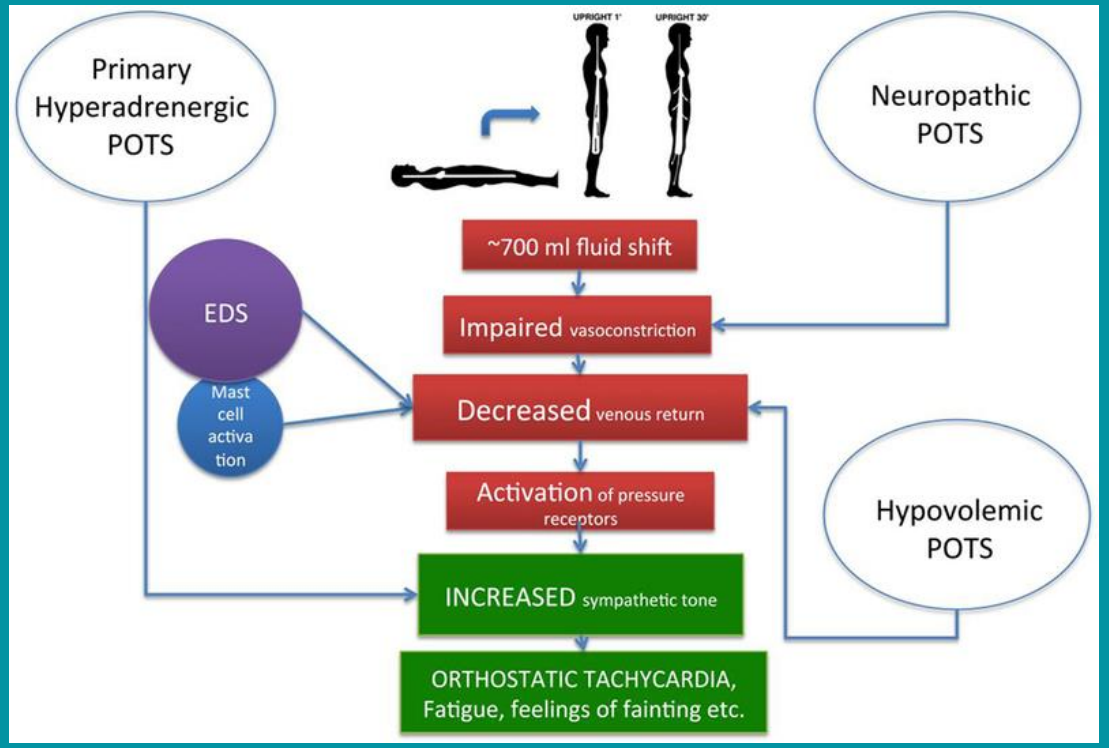
About 80% good response

What is POTS?
There are various forms of POTS

- I. **Neuropathic POTS**: could be immune-mediated

- **II. Hyperadrenergic POTS**: Overactivity of the sympathetic nervous system or Imbalance between sympathetic or para-sympathetic activity

- **III. Low blood volume POTS**: Reduced blood volume can lead to POTS.



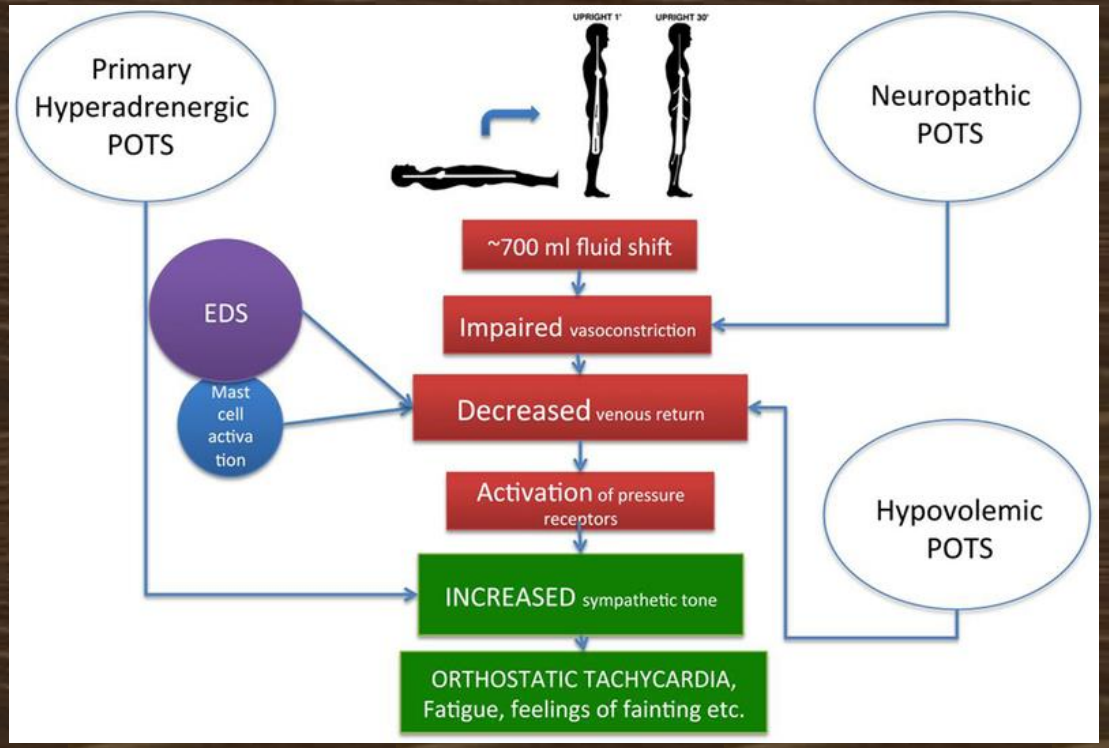
What is POTS?
There are various forms of POTS

- **I. Neuropathic POTS**: could be immune-mediated

- **II. Hyperadrenergic POTS**: Overactivity of the sympathetic nervous system or Imbalance between sympathetic or para-sympathetic activity

- **III. Low blood volume POTS**: Reduced blood volume can lead to POTS.

- **IV. Central POTS (???,my classification)**: Good response to SSRI treatment.



What are the symptoms of POTS?

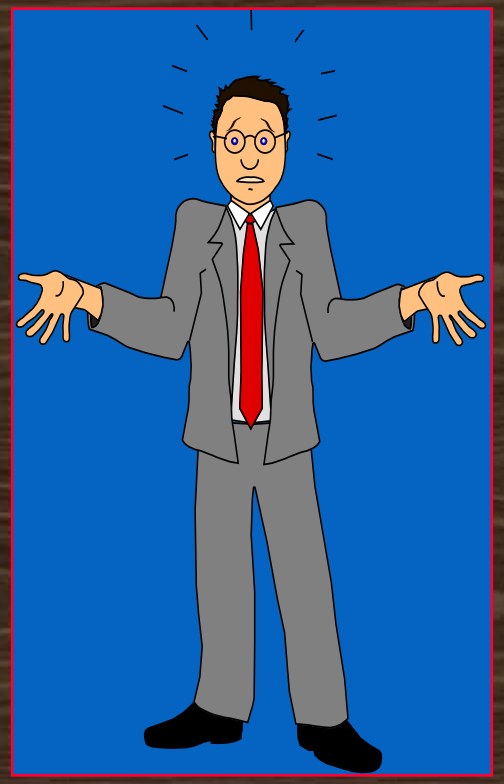
POTS usually suffer from two or more of the many symptoms listed below.
Not all patients with POTS have all these symptoms.

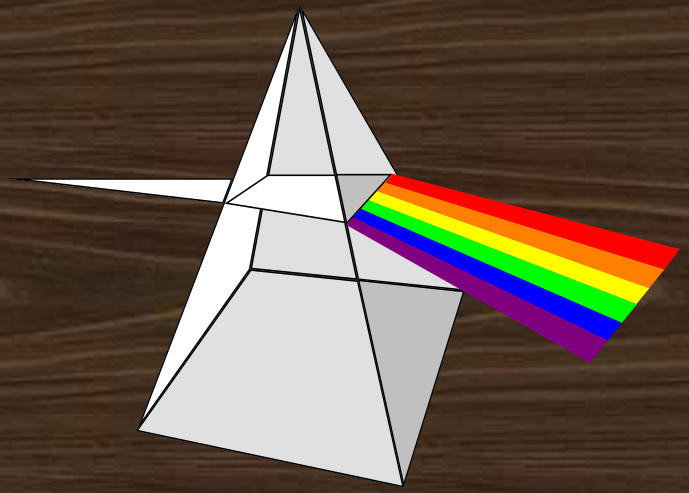
- Dizziness/lightheadedness ?
- Earthquake-like feeling ?
- Fainting/syncope ?
- Blurred vision ?
- Exhaustion/fatigue
- Chest pain
- Abdominal pain and bloating

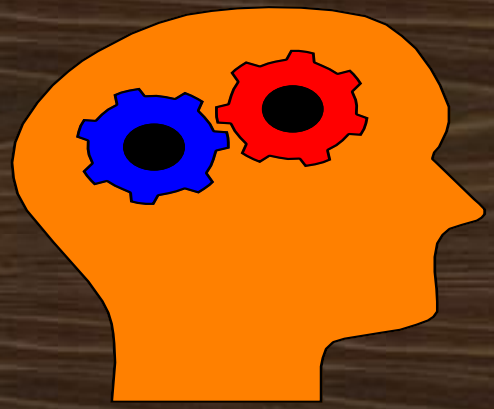
- Trouble focusing (brain fog)
- Nervous, jittery feeling
- Insomnia
- Shakiness/tremors
- Discoloration of feet and hands
- Exercise intolerance

CBF and Balance in POTS

- I feel dizziness, lighted-headed, visual blurring, tremulousness and palpitation after standing up

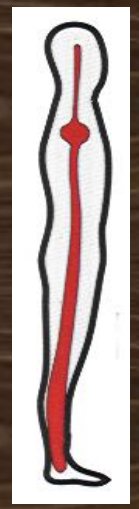


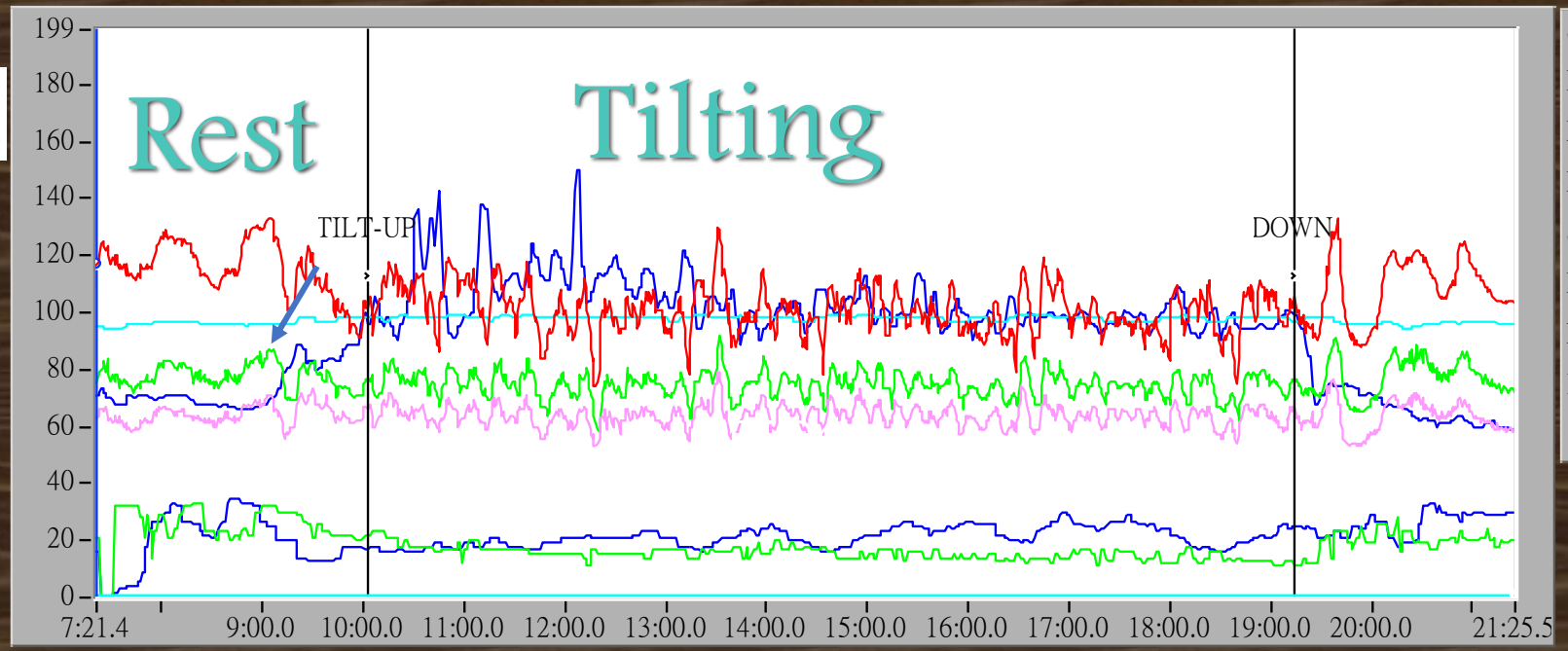


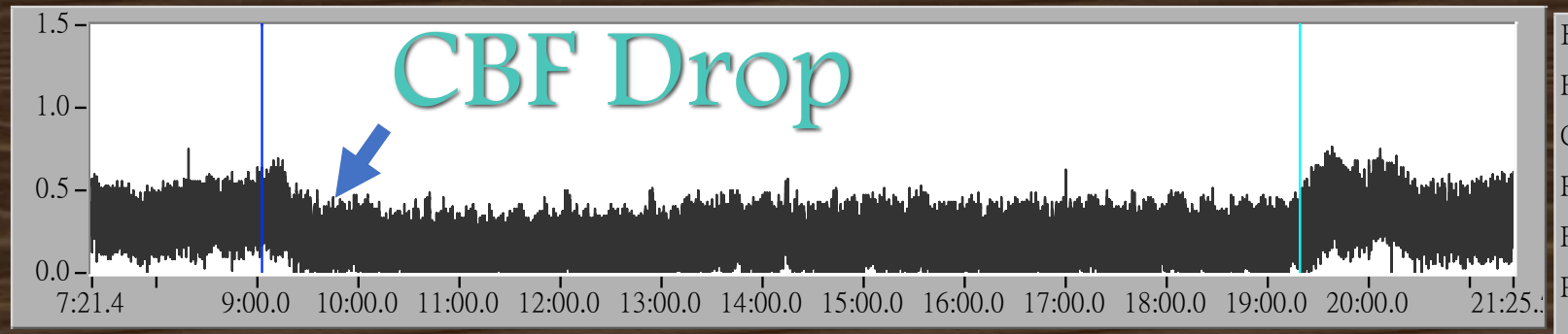


What happens to me? Why?

CBF Drop from Rest to Tilting in POTS







Data of CBF and CO2 Change during Head-Up Tilting (HUT) in Controls and POTS

Clinical Features

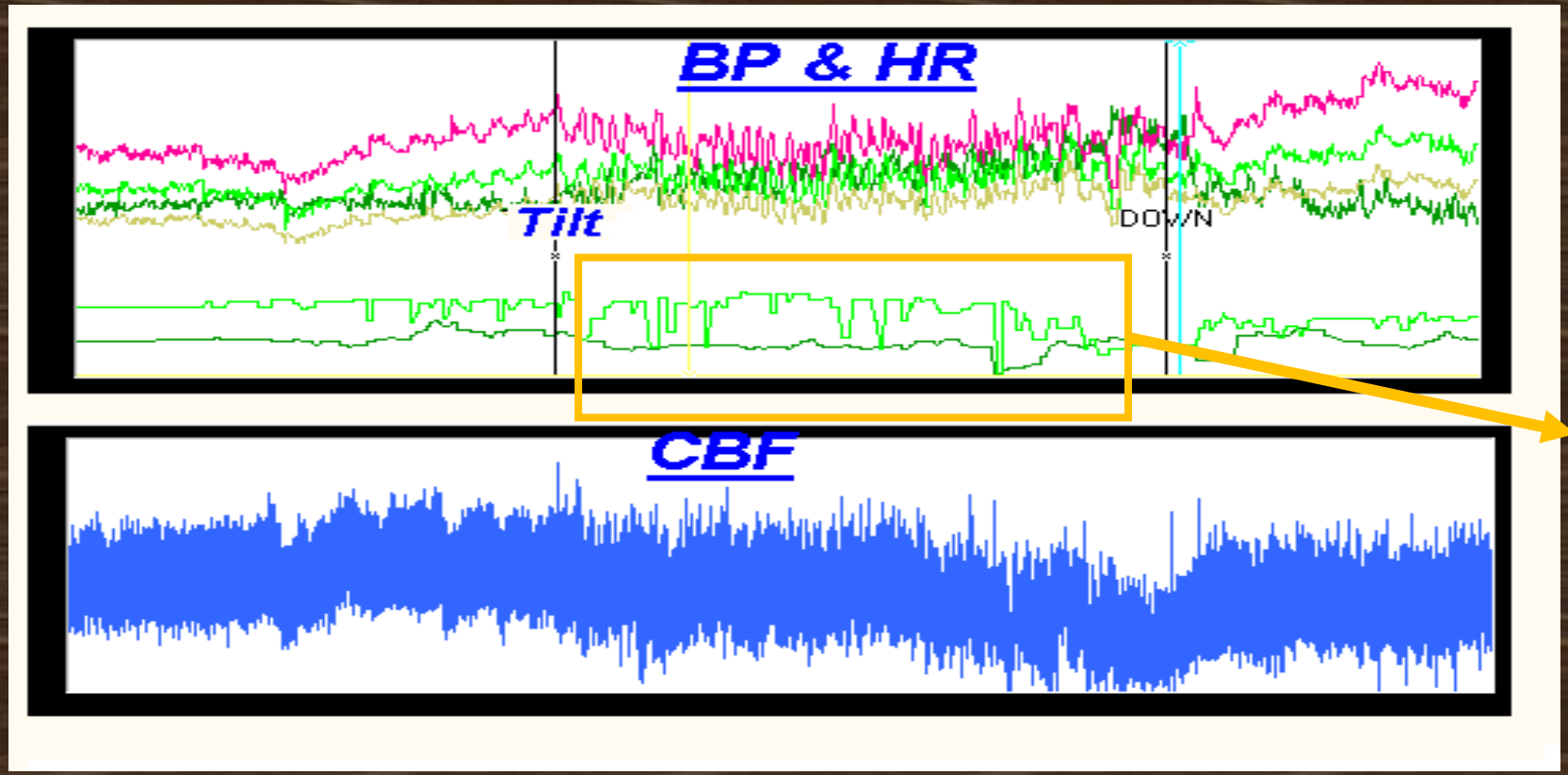
	Control	POTS
◆ Number	10	10
◆ Age	33.7 ± 6.16	35.1 ± 8.06
◆ Sex (M:F)	3 : 7	3 : 7

Results:

	Baseline				HUT				ROC	
	CO2	SBF	MBF	PI	CO2	SBF	MBF	PI	SBF	MBF
Cont	33.4*	83.1	57.9	0.68	28.3*	72.5	51.9	0.71	0.12*	0.10*
POTS	29.3	80.2	55.8	0.77	21.2	58.8	39.3	0.89	0.27	0.29

All data are mean values; * $p < 0.05$ (t-test);
ROC= ratio of change

Cerebral Regulation and Systemic Hemodynamic Change during Tilting in POTS



Comparisons of the Nonlinear Relationship of Cerebral Blood Flow Response and Cerebral Vasomotor Reactivity to Carbon Dioxide under Hyperventilation between Postural Orthostatic Tachycardia Syndrome Patients and Healthy Subjects

Shyan-Lung Lin 1,* , Shoou-Jeng Yeh 2, Ching-Kun Chen 1, Yu-Liang Hsu 1 , Chih-En Kuo 1 ,Wei-Yu Chen 1 and Cheng-Pu Hsieh 1

Linear analysis

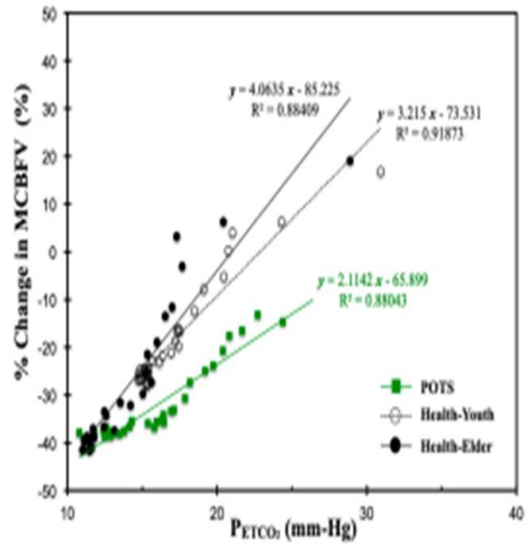


Figure 6. Linear analysis of averaged percentage change in MCBFV to CO_2 for the three subject groups during 30 s of hyperventilation.

Nonlinear model analysis

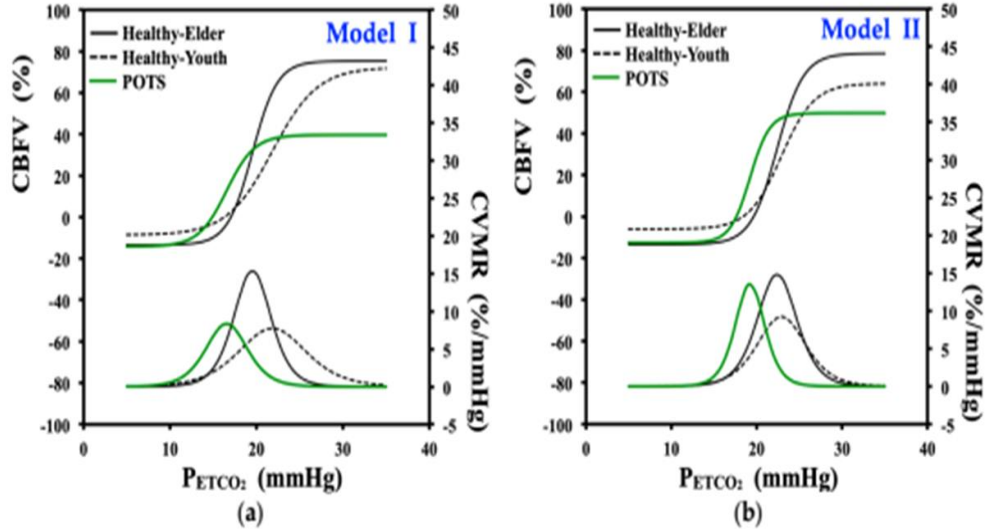


Figure 7. Nonlinear curve fit results of percentage change in CBFV responses to CO_2 (P_{ETCO_2}) during hyperventilation for the three subject groups: (**a**) nonlinear regression with curve-fitting Model I of Equation (2); (**b**) nonlinear regression with Model II of Equation (3).

J. Clin. Med. 2020, *9*, 4088 ;doi:10.3390/jcm9124088

Propranolol Decreases Tachycardia but does not Improve Postural Stability and Cerebral Blood Flow in the Postural Orthostatic Tachycardia Syndrome

Dr. Shoou-Jeng Yeh[1]

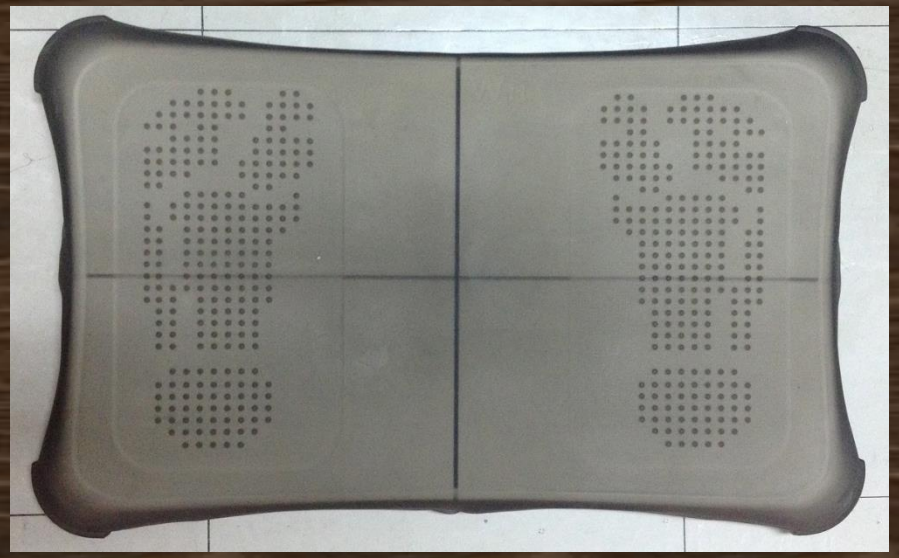
Dr. Chuang-Chien Chiu[1,2]

Che-Wei Su[3]

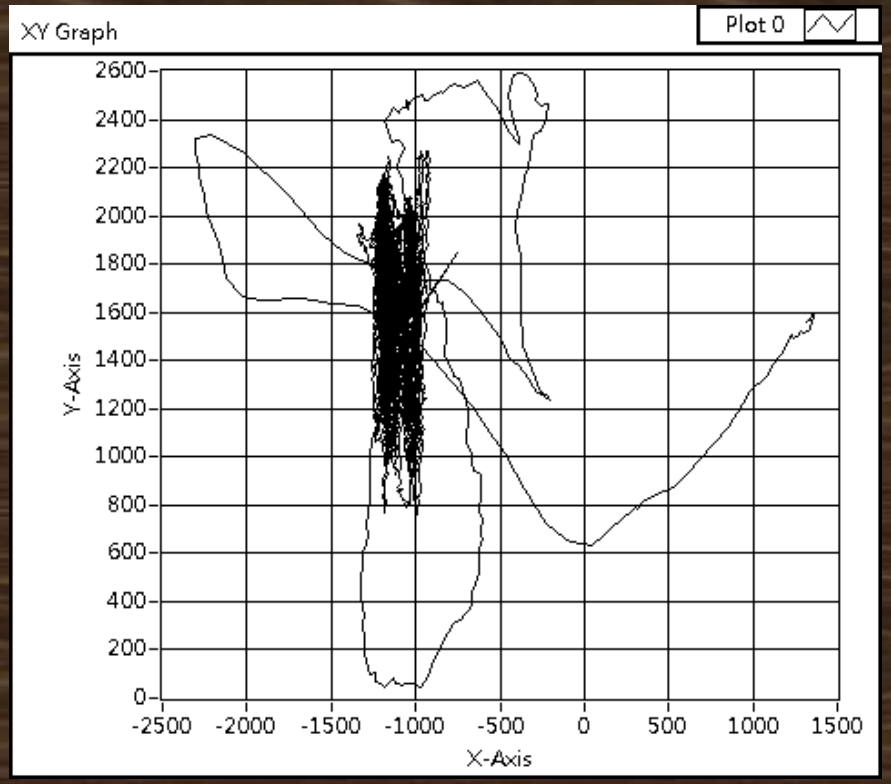
[1] Section of Neurology and Neurophysiology, Taichung Cheng Ching General Hospital, Taiwan
[2] Department of Automatic Control Engineering, Feng Chia University, Taiwan
[3] Ph.D. Program of Electrical and Communications Engineering, Feng Chia University, Taiwan

Our Study about POTS Postural Stability

Quantitative postural stability by Center of Pressure



Stabilogram



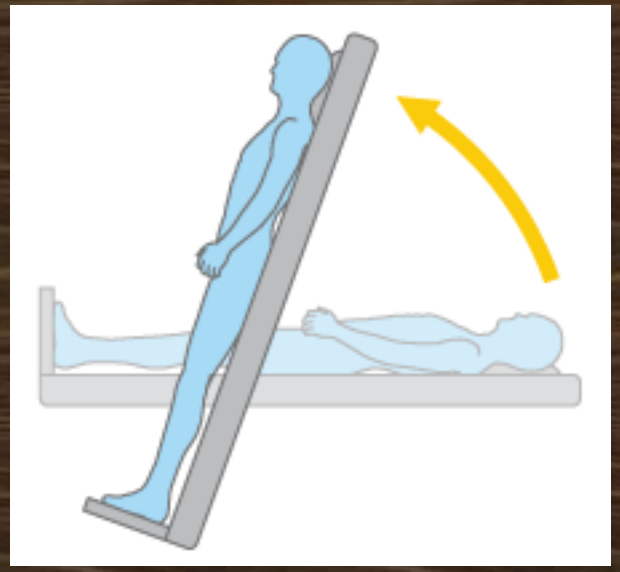
Subjects

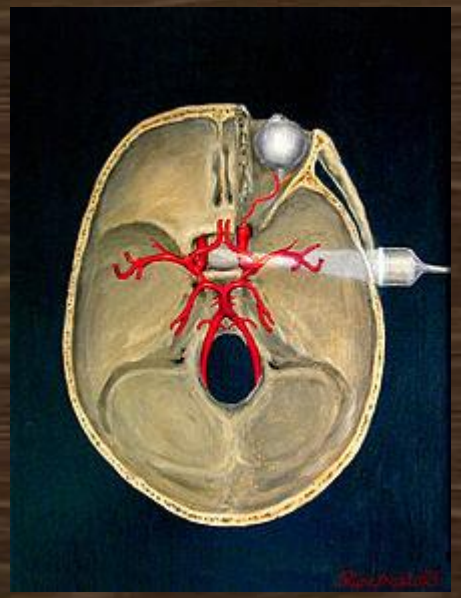
- Cheng Ching General Hospital
- Patients met criteria for POTS
- Fourteen Subjects, 8 female and 6 male
- Age : 29.21±8.37

Our Study about POTS Cerebral Blood Flow Drop % Normal Subjects vs POTS in Tilt Table Test

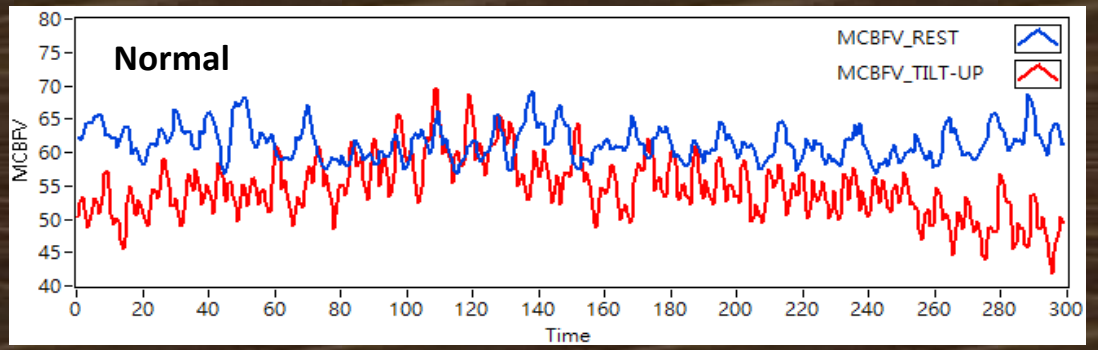
Tilt Table Test

Transcranial Doppler





Cerebral Blood Flow



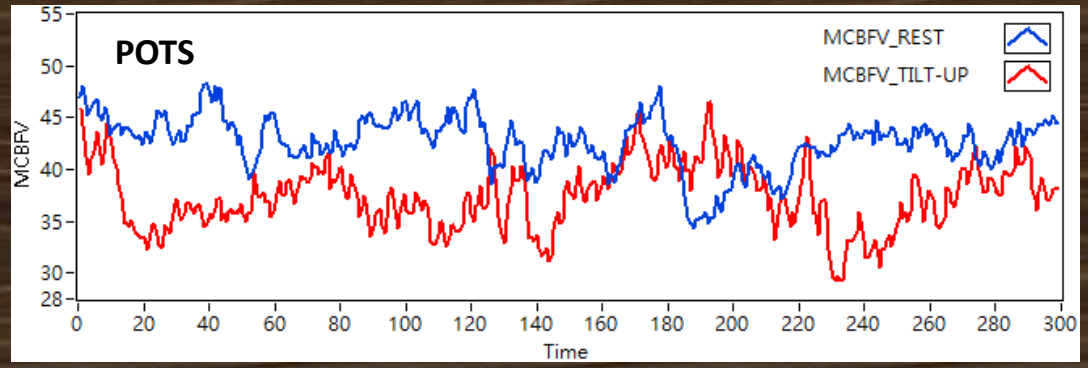
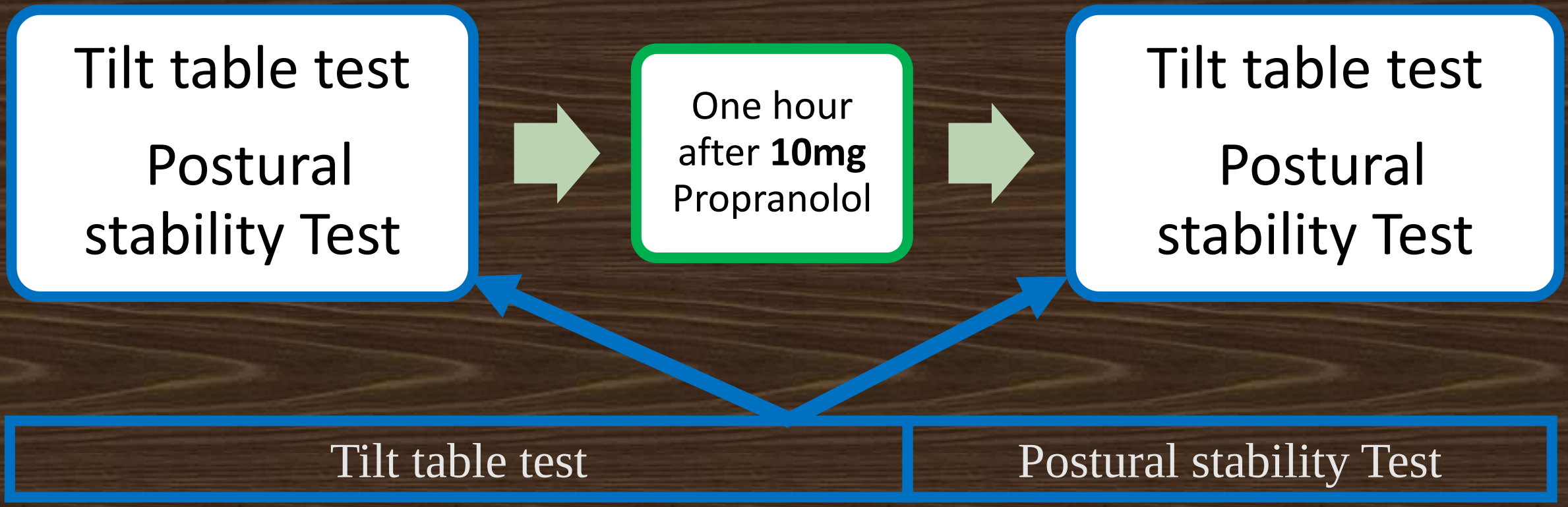


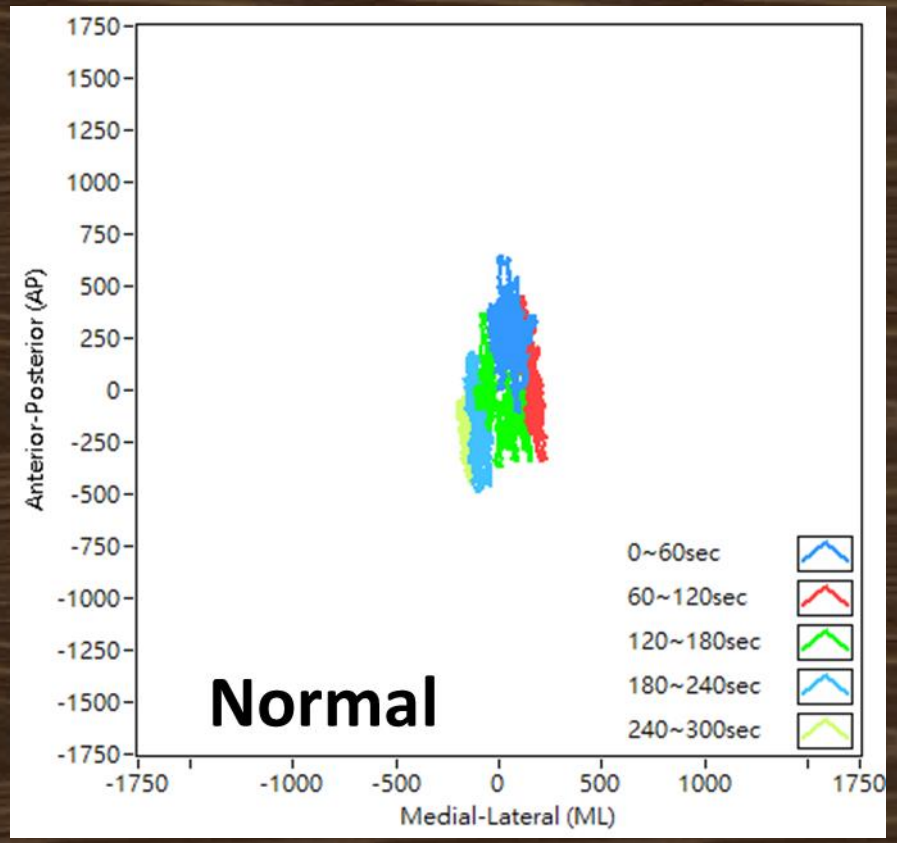
Image Source :
Web site of Cardiac Electrophysiology Laboratory
Transcranial Doppler, http://en.wikipedia.org/wiki/Transcranial_Doppler

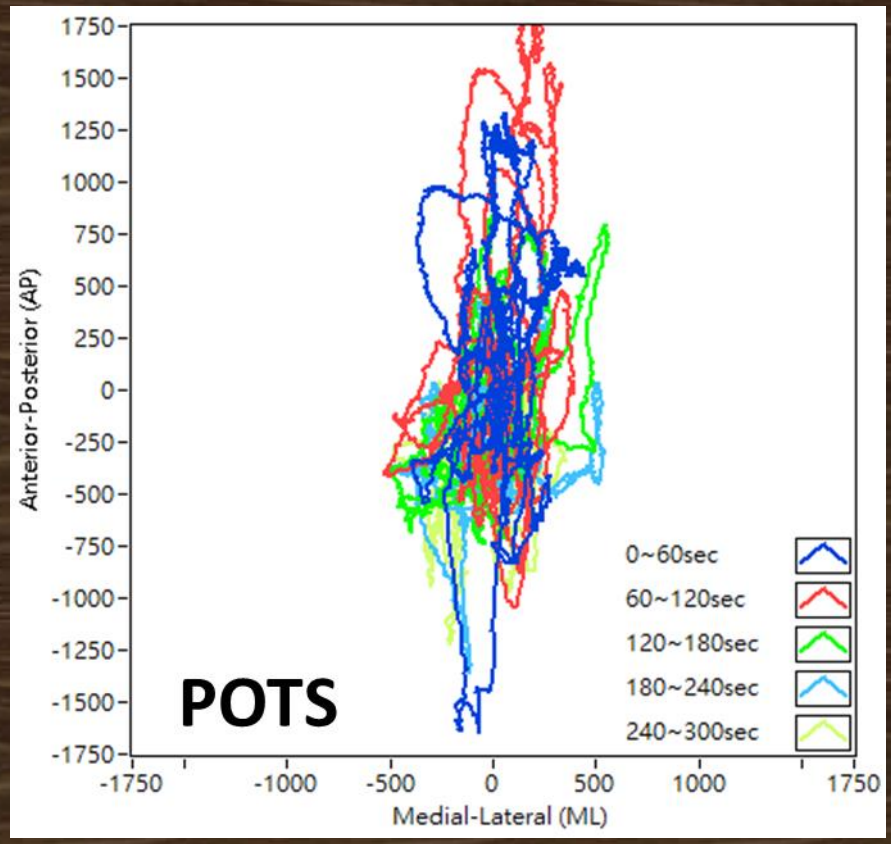
Method



Tilt table test	Postural stability Test
• Head-up tilt, 10 minutes • Continuous Heart Rate • Continuous Non-invasive Arterial Pressure • Cerebral Blood Flow	• Quiet standing, 5 minutes • Center of Pressure

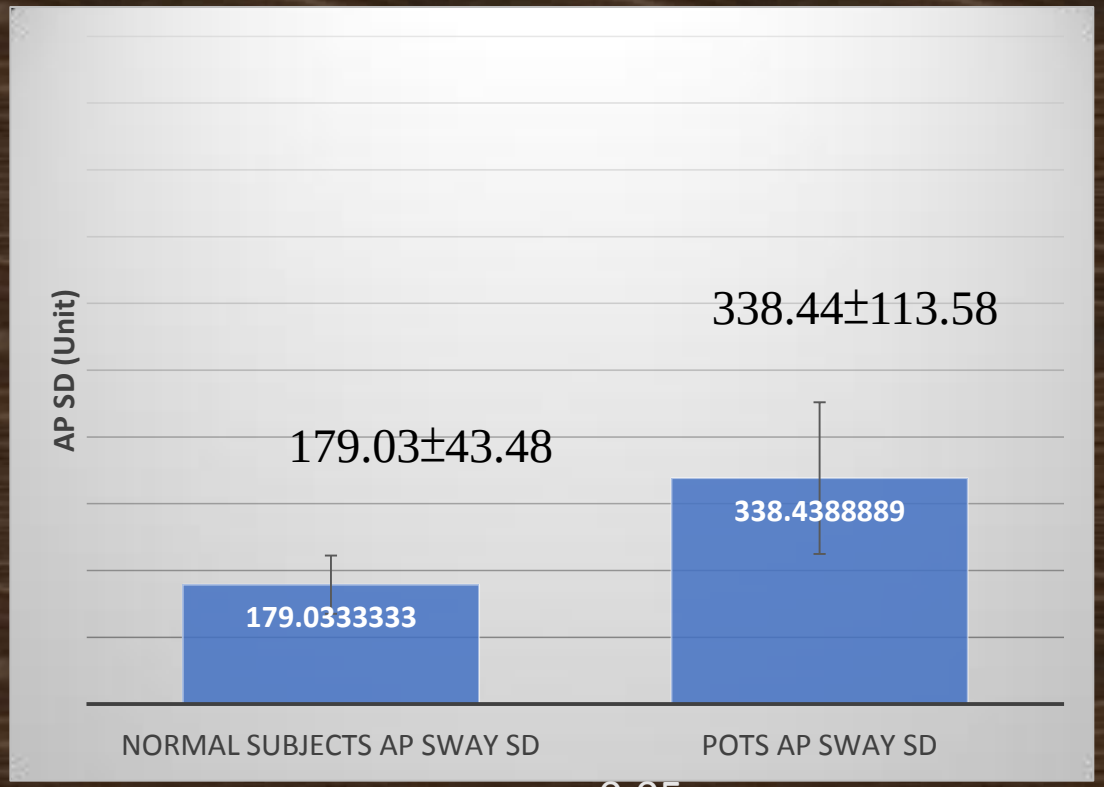
Our Study about POTS Postural Stability
Normal Subjects vs POTS Stabilogram





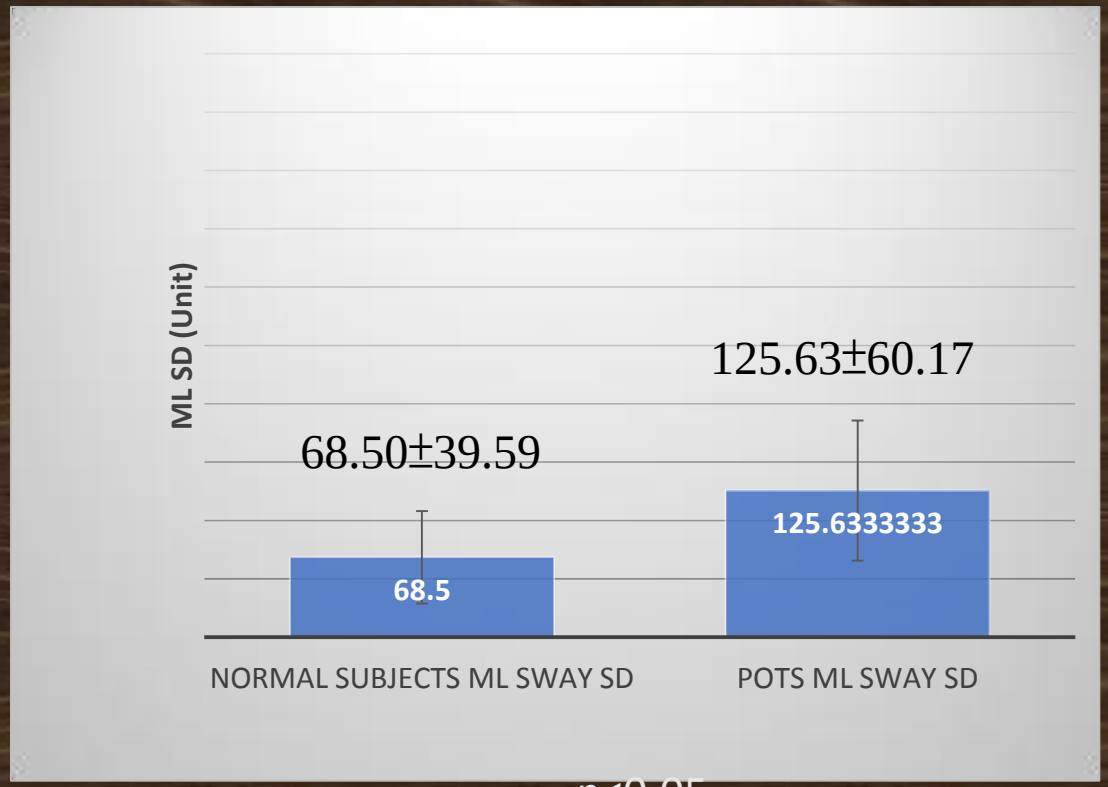
Our Study about POTS Postural Stability

Anterior-posterior (AP, ↕) sway



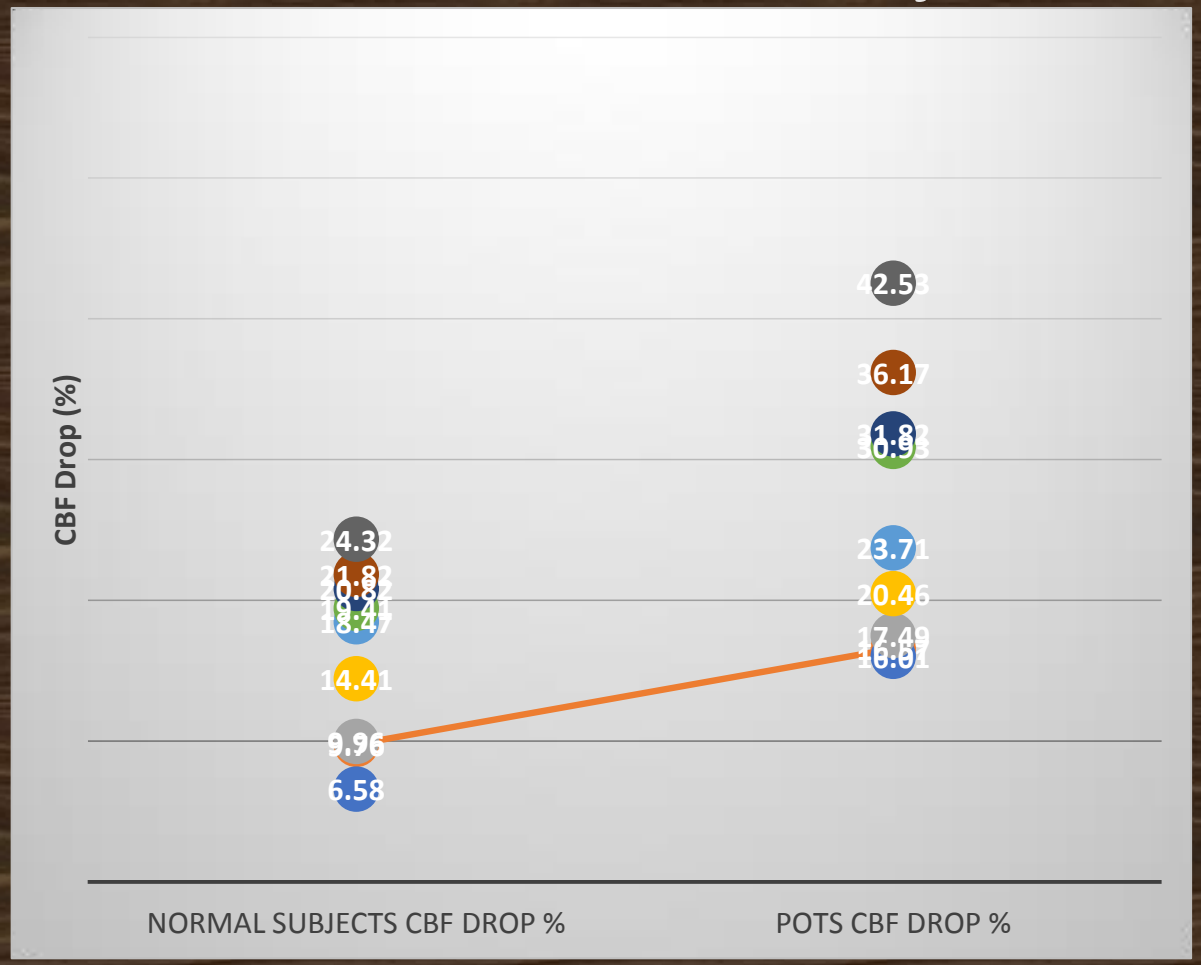
$p<0.05$

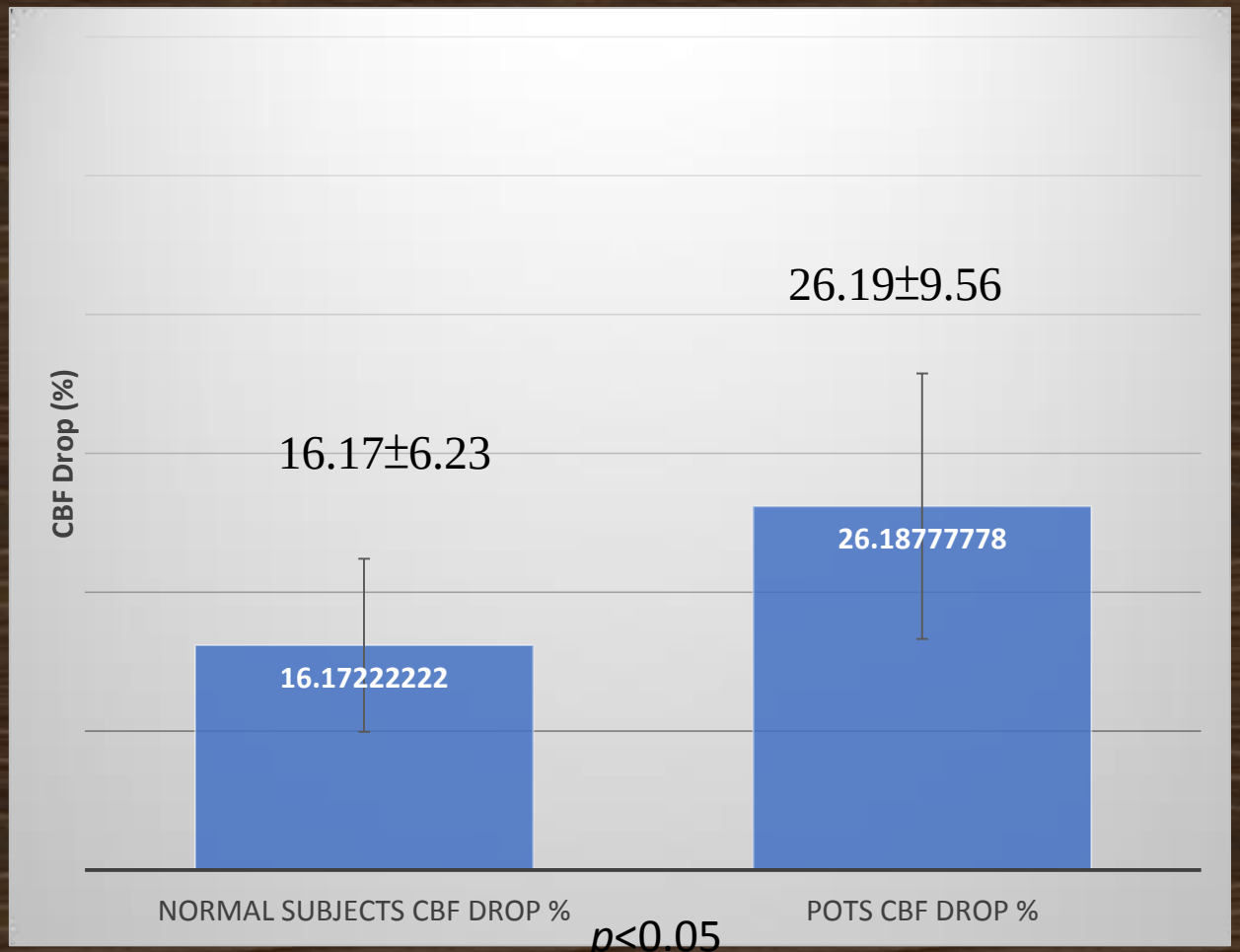
Medio-lateral (ML, ↔) sway



$p<0.05$

Our Study about POTS Cerebral Blood Flow Drop %
Normal Subjects vs POTS in Tilt Table Test



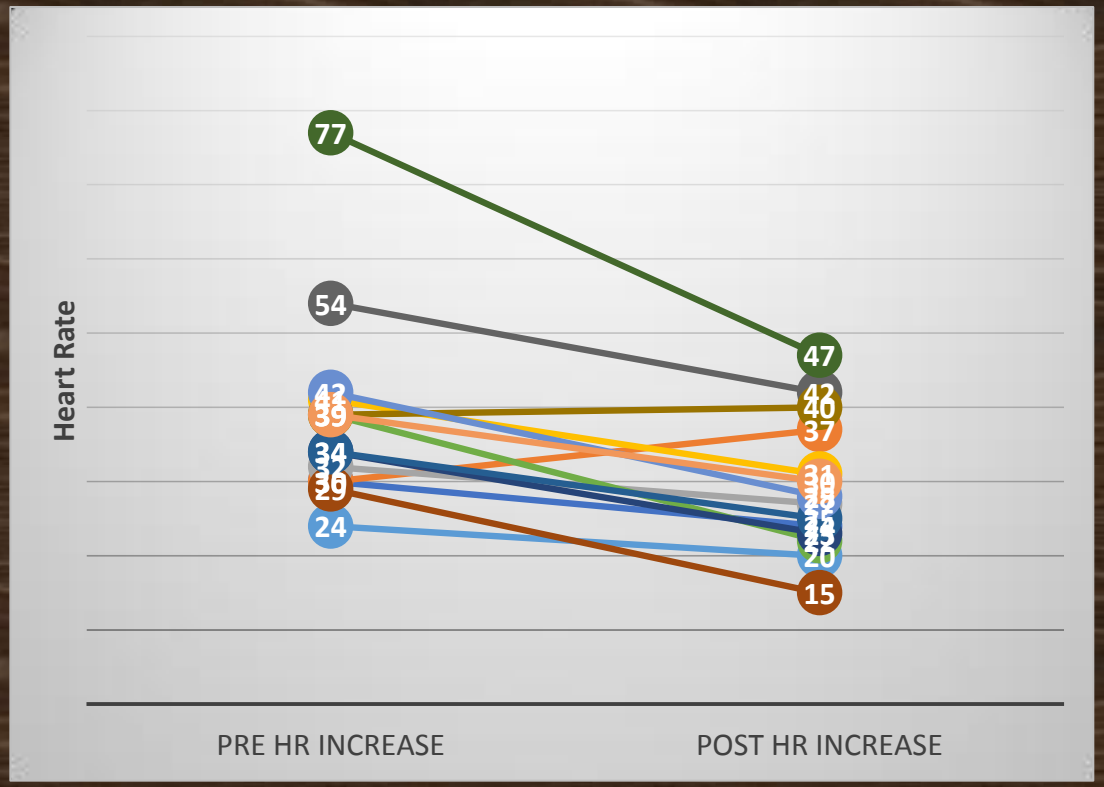


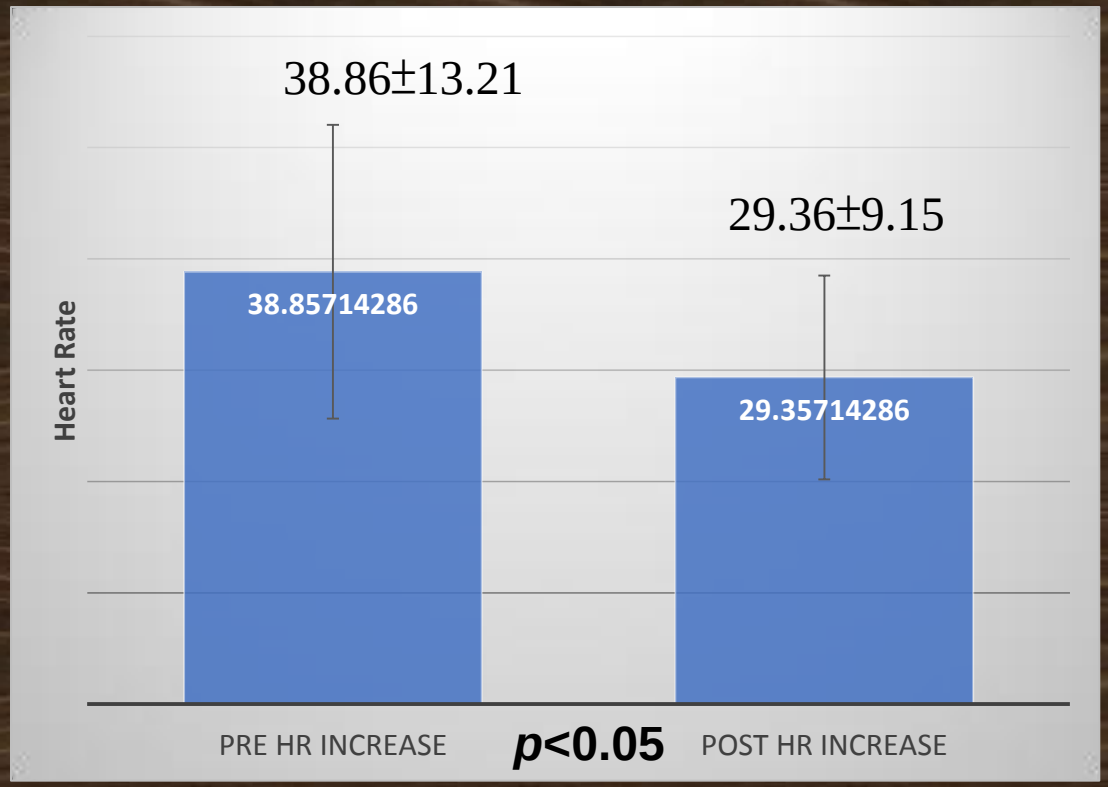
$p<0.05$

Result – Tilt-up Heart Rate Increase Change

HR Increase Change

Before and one hour after 10 mg Propranolol

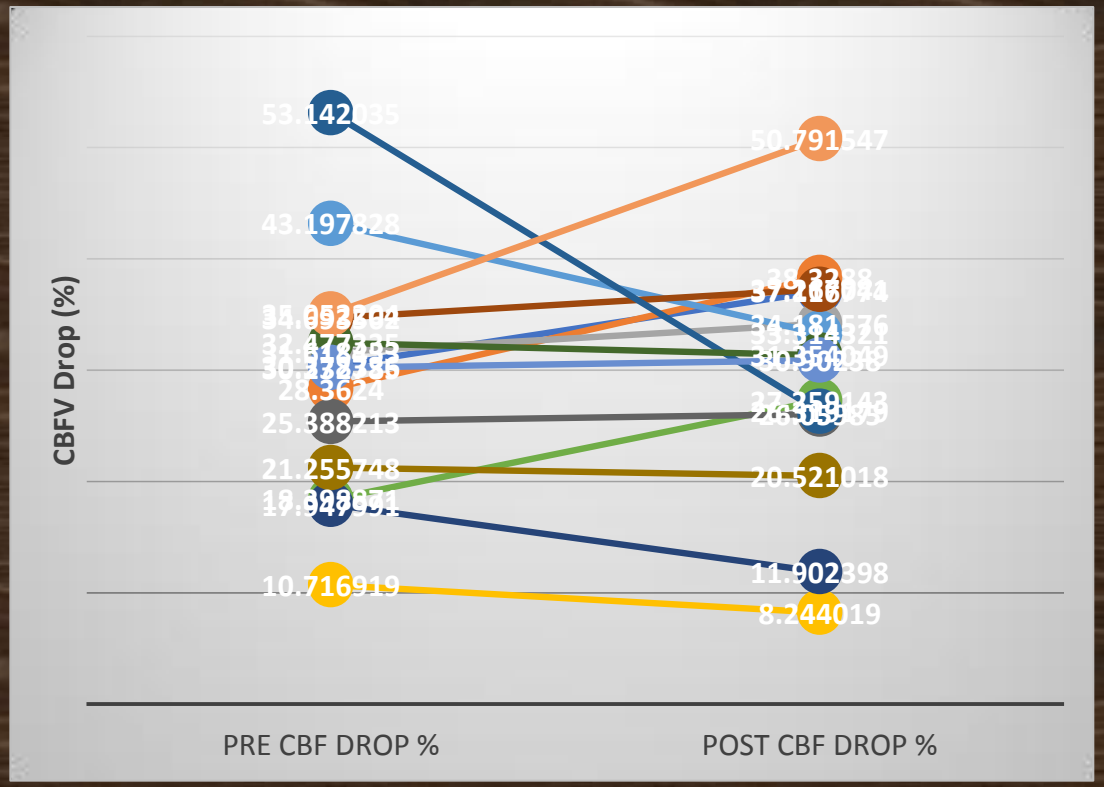


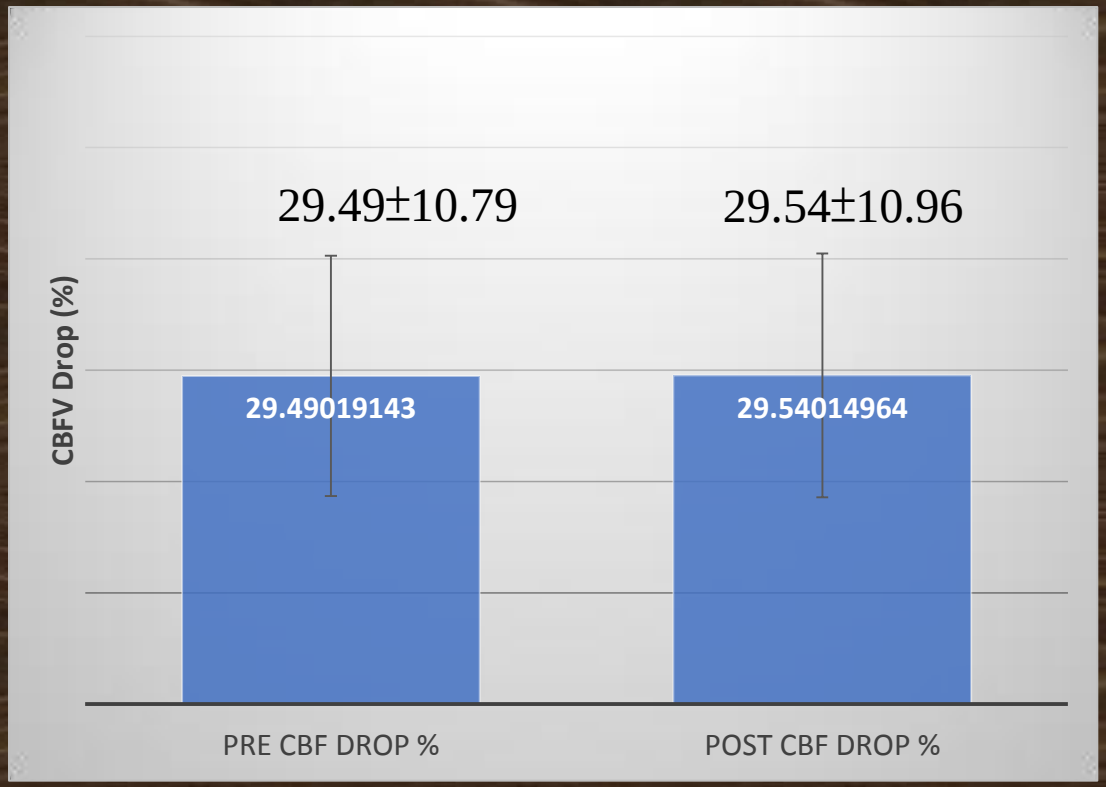


Result - Cerebral Blood Flow

Cerebral Blood Flow Drop (%)

Before and one hour after 10 mg Propranolol

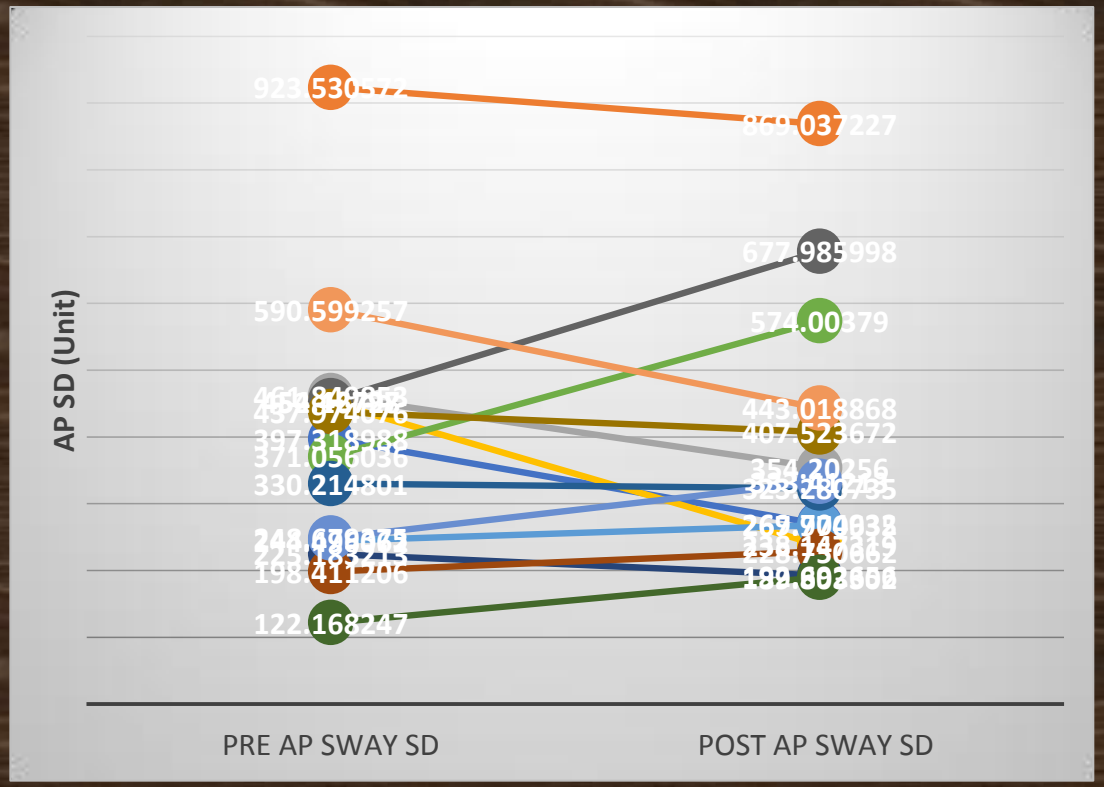


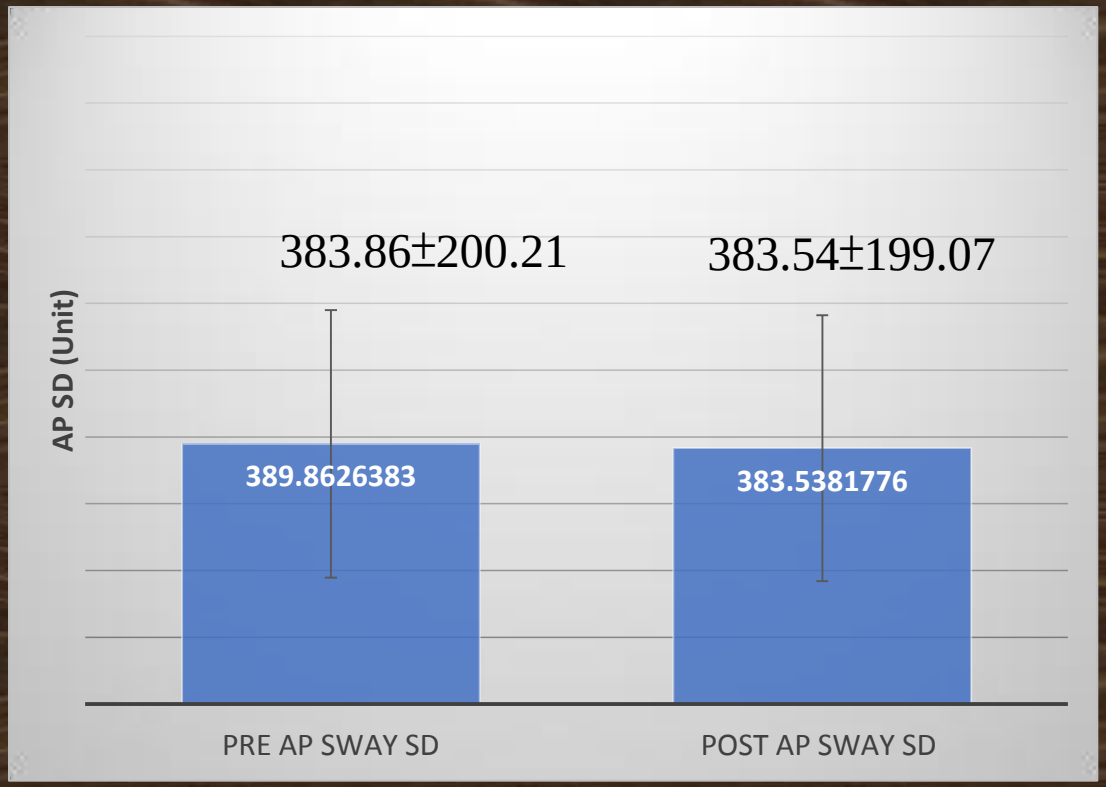


Result – Postural Stability

AP(↕) sway of center of pressure

Before and one hour after 10 mg Propranolol

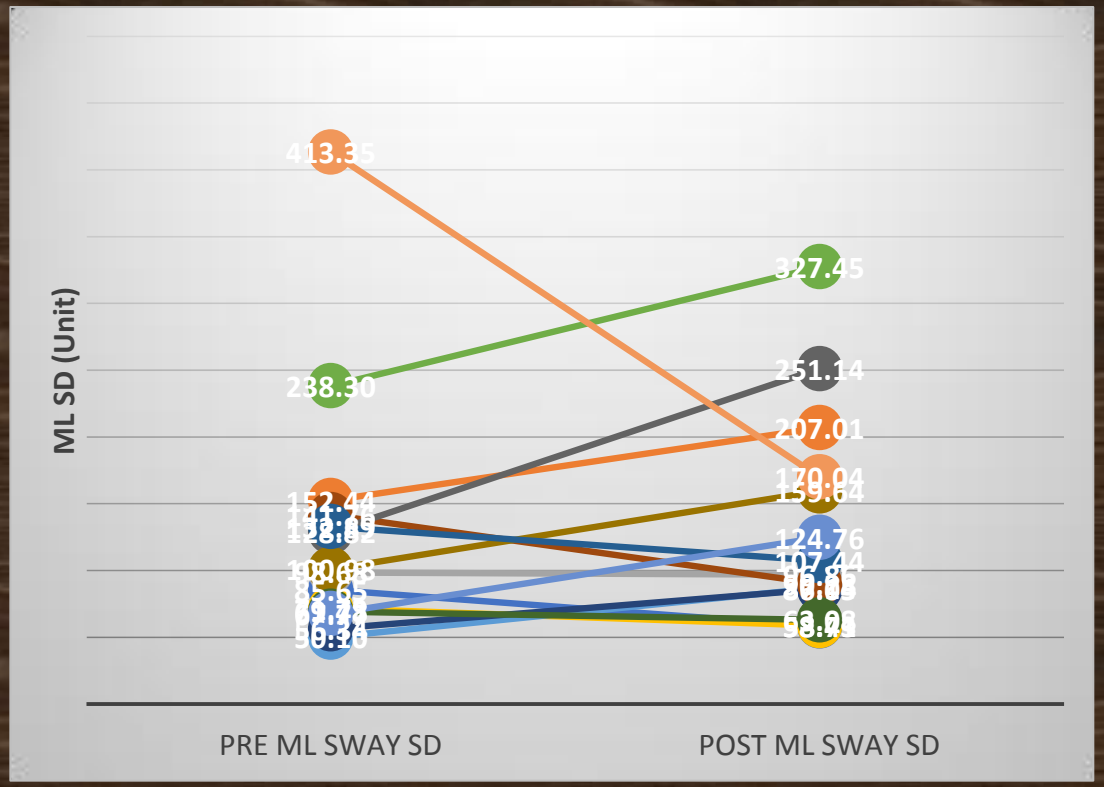


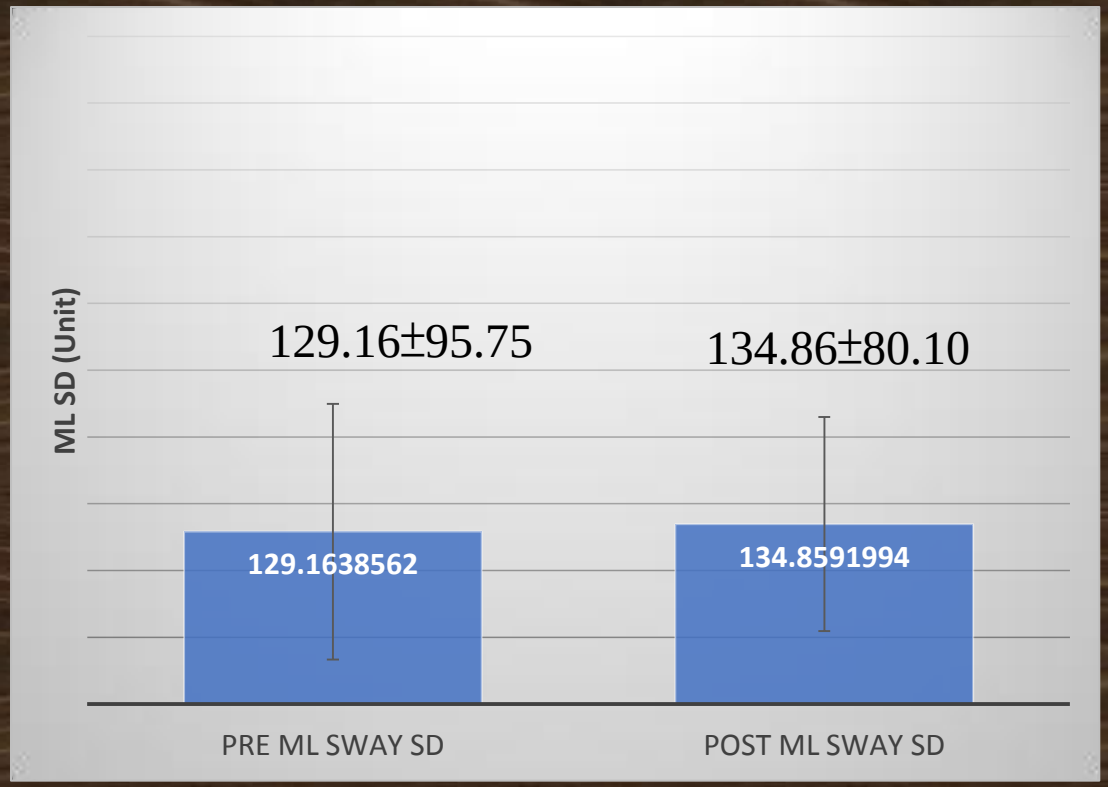


Result – Postural Stability

ML(↔) sway of center of pressure

Before and one hour after 10 mg Propranolol





Conclusions

After one hour low-dose propranolol (10mg) :

May attenuate orthostatic tachycardia

May not improve cerebral blood flow and postural stability

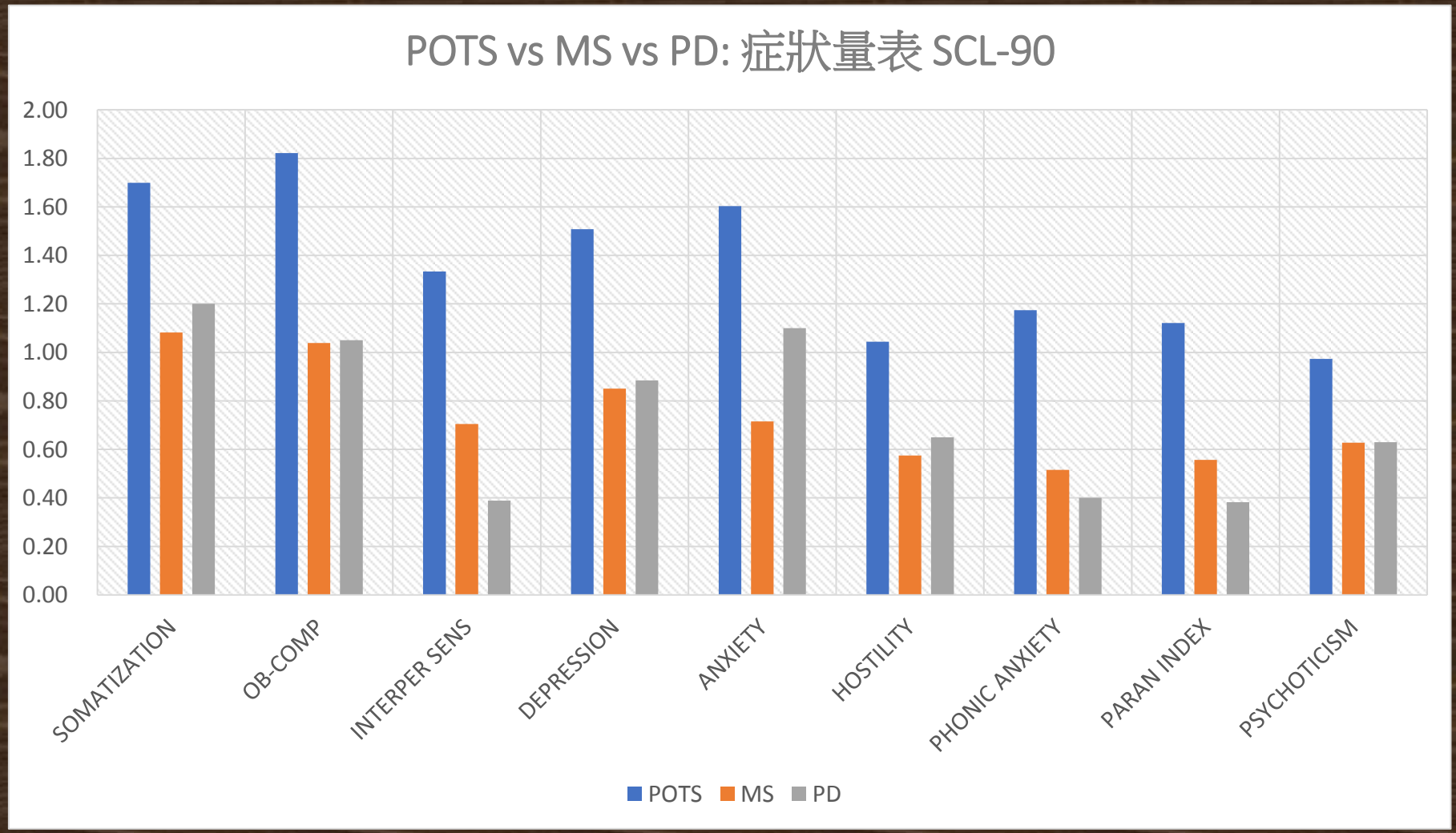
症狀自評量表-SCL90 in various forms of POTS

- 《症狀自評量表SCL90》是世界上最著名的心理健康測試量表之一，是當前使用最為廣泛的精神障礙和心理疾病門診檢查量表，將協助 您從十個方面來了解自己的心理健康程度

- 90項症狀清單（SymptomChecklist90，SCL-90），又名症狀自評量表（Self-reportingInventory) 。於1975年編制，其作者是德若伽提斯（L.R.Derogatis)。該量表共有90個項目。

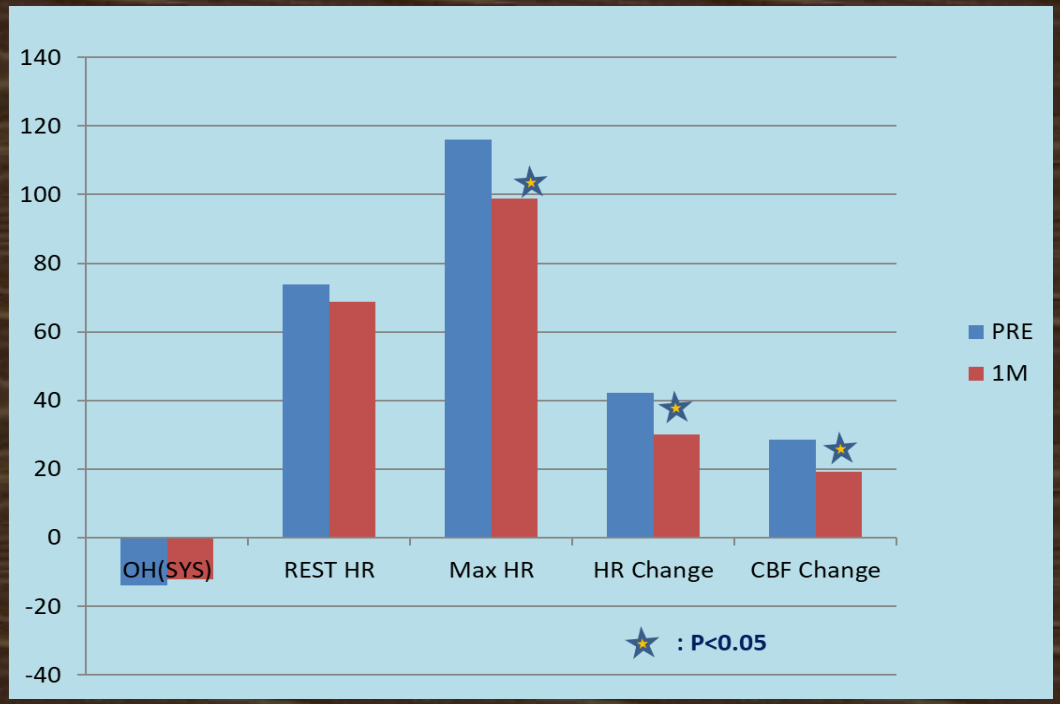
- 共9個分量表，即軀體化、強迫症狀、人際關係敏感、抑鬱、焦慮、敵對、恐怖、偏執和精神病性。

POTS廣泛的精神障礙和心理疾病
Typical POTS vs MS vs PD POTS

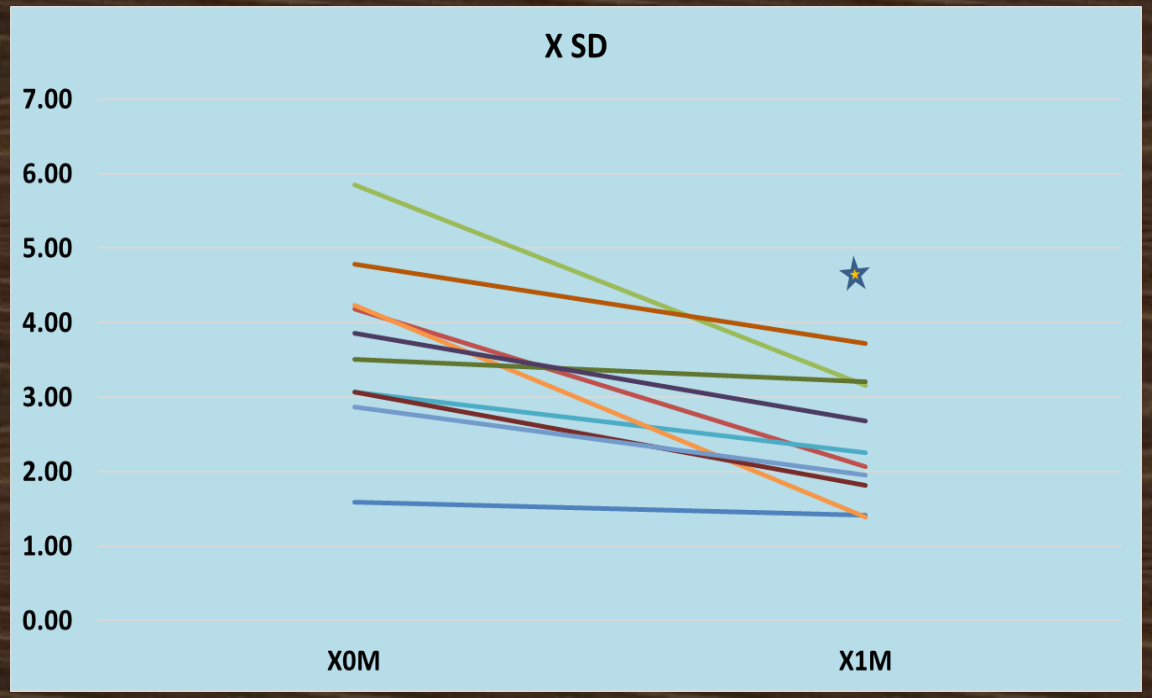


Significant improvement of HR, CBF and Balance Sway Change during Tilting After one Month of SSRI Treatment

HR and CBF Change during Tilting before and after one Month of SSRI Treatment



Balance Sway Change during Tilting before and after one Month of SSRI Treatment

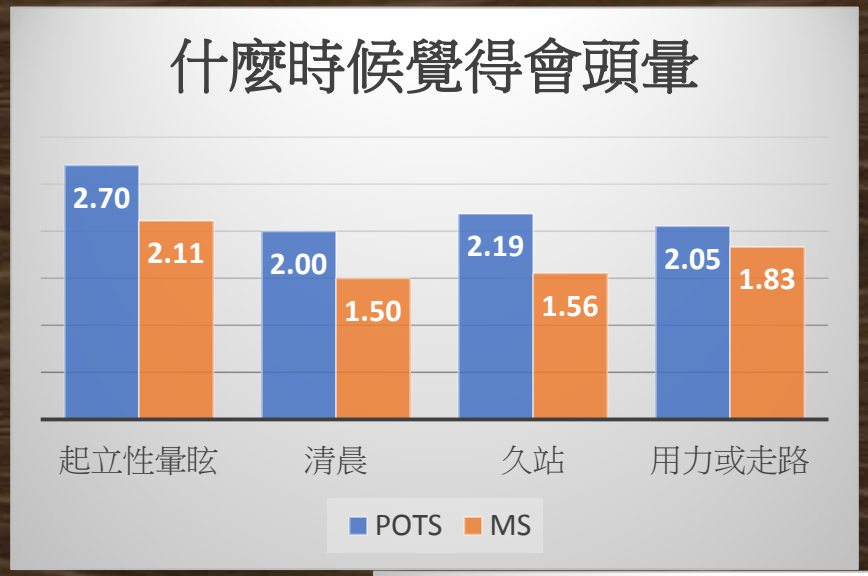


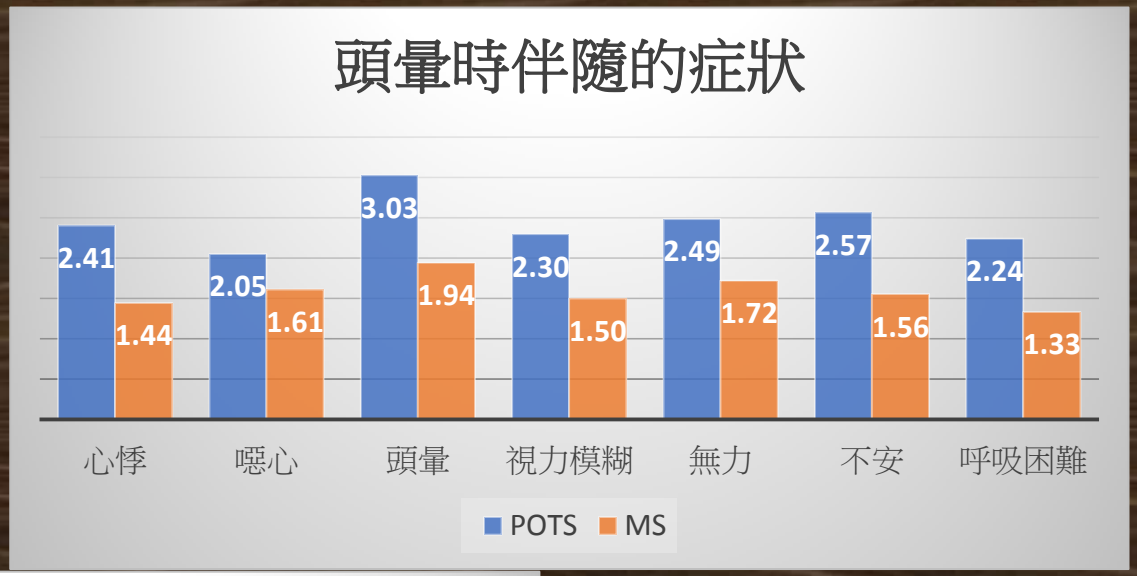
X(M-L) T-Test = 0.001335053

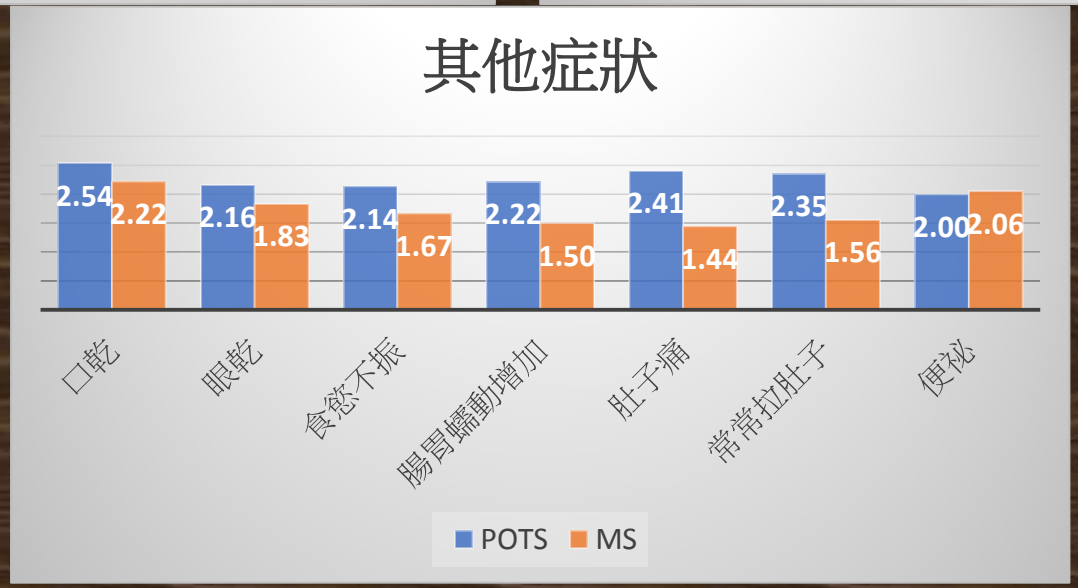
10 Subjects of POTS
Mean Age = 25.9 y/o ± 5.3
F:M = 5:5

Unpulished Data from our Lab.

Dizziness in Autonomic Questionnaire
POTS vs MS







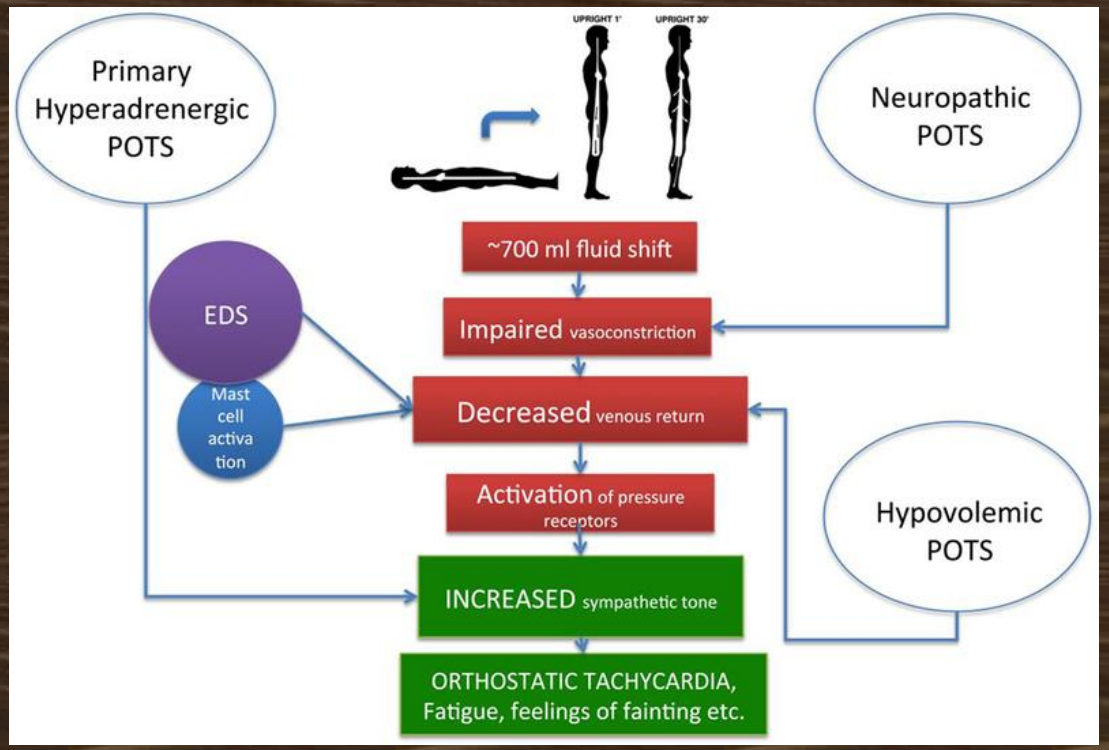
Conclusions

- Low-dose oral propranolol may attenuate tachycardia
- Not improved cerebral blood flow and postural stability
- cerebral blood flow and postural stability improved by SSRI
- Higher Psychomotor Scores In POTS

----------> Brain Central Effect?

What is POTS?
There are various forms of POTS

- **I. Neuropathic POTS**: could be immune-mediated
- **II. Hyperadrenergic POTS**: Overactivity of the sympathetic system.
- **III. Low blood volume POTS**: Reduced blood volume can lead to POTS.
- **IV. Central POTS (my classification)**: most typical young lady POTS



POTS in CNS Disease

- Multiple Sclerosis in early stage
- Early Parkinson's Disease

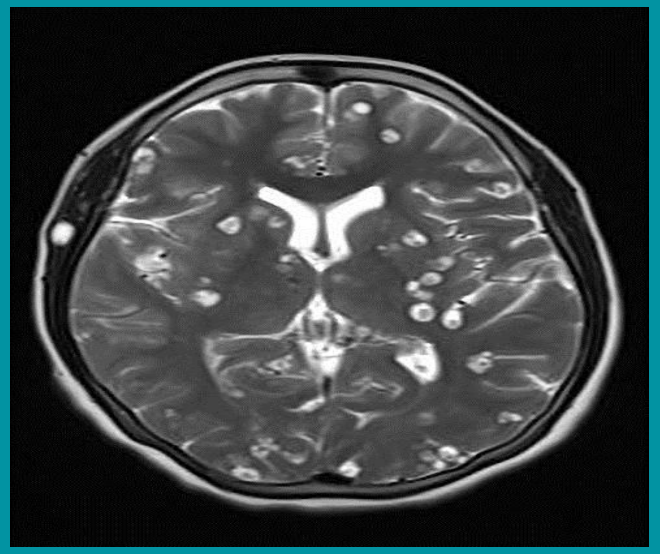
MS-Case 1

5864005 朱0 19 y/o (F)

- First diagnosed as Neurocysticercosis and received brain biopsy in one of the medical center.
- Was later diagnosed as Multiple Sclerosis

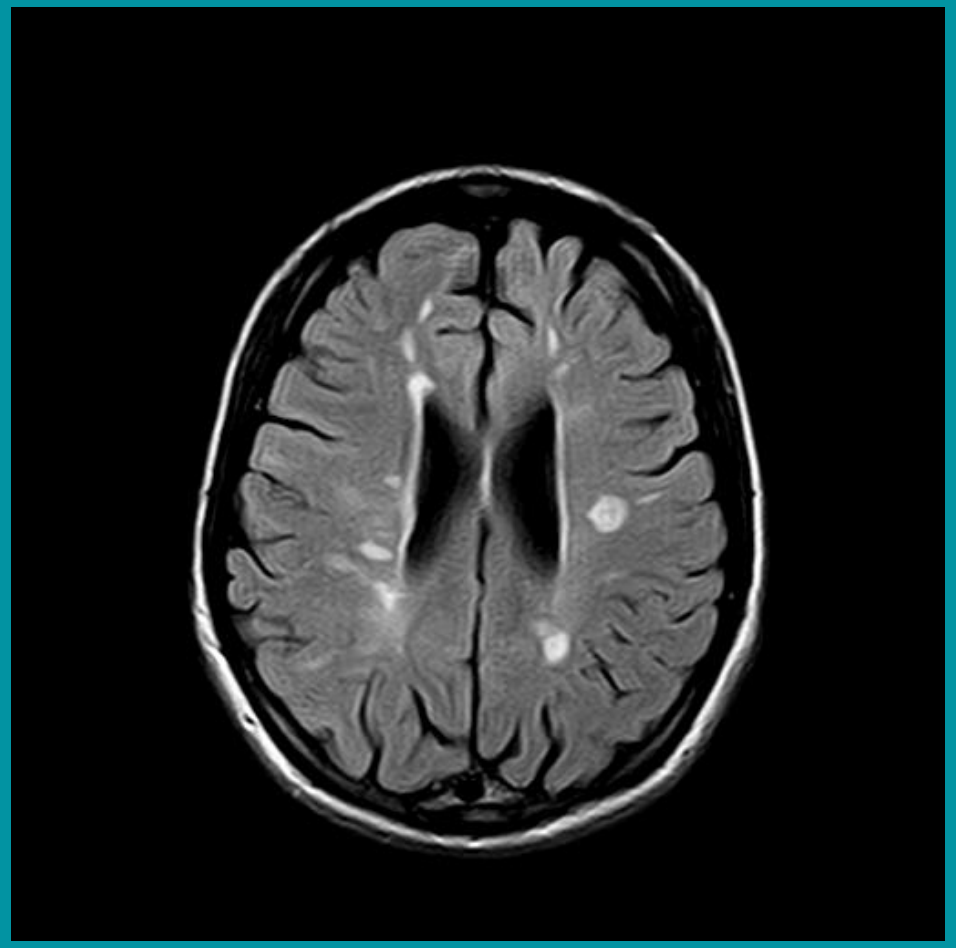
Neurocysticercosis

from Google

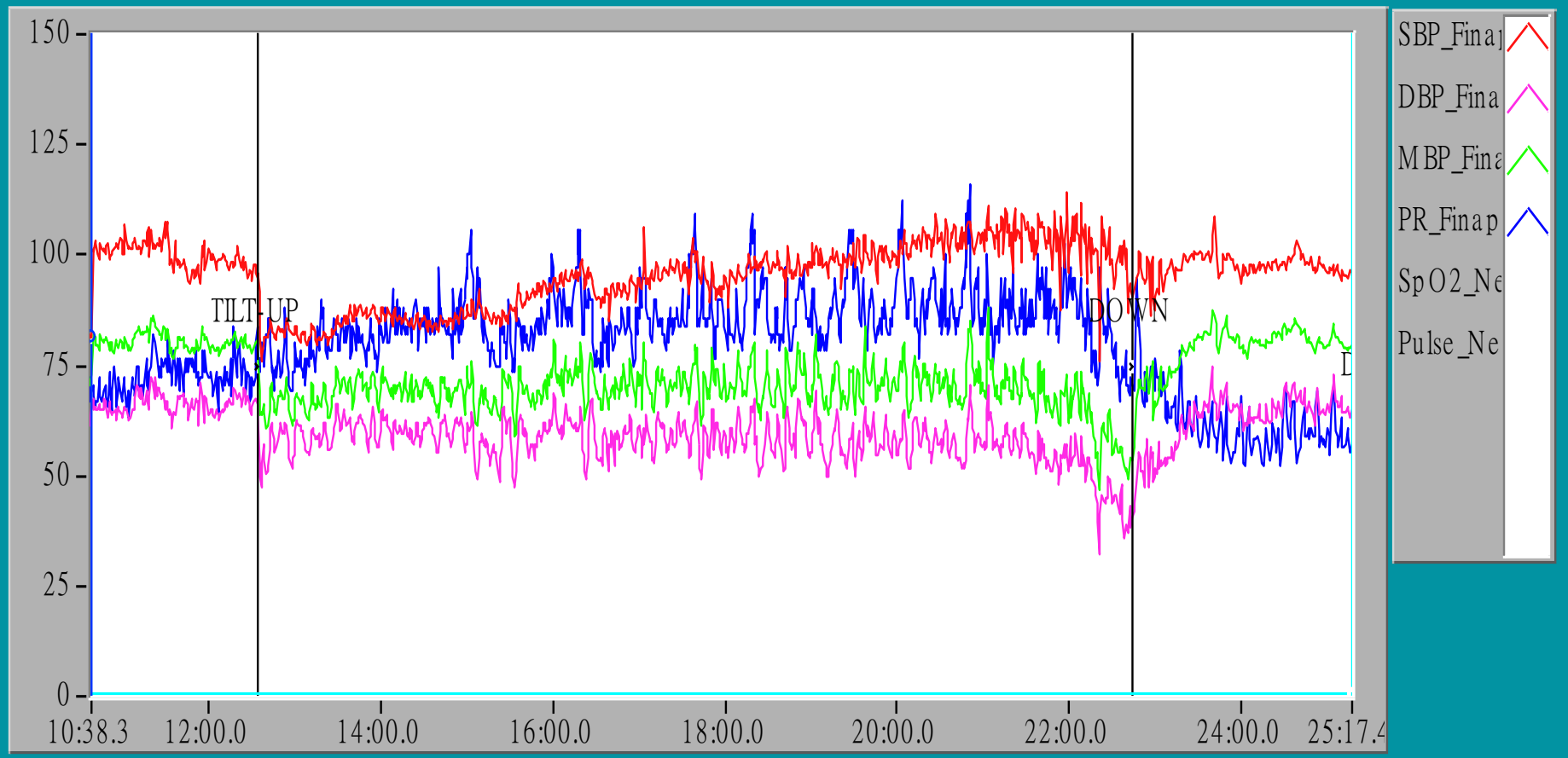


MRI Findings

5864005 朱0 19 y/o (F)



MS-TILTING TABLE TEST



5864005 朱0 19 y/o (F)

The Percentage of POTS in Our Cases of Multiple Sclerosis < 45 y/o after Tilting Table Test and ANS Questionnaire

	NL	Borderline	POTS	TOTAL
N0 (M/F)	8(3/5)	6(1/5)	7(2/5)	21(6/15)
Age	30.5	30.9	31.2	31.1
比例	38.09%	28.57%	33.33%	

>60%

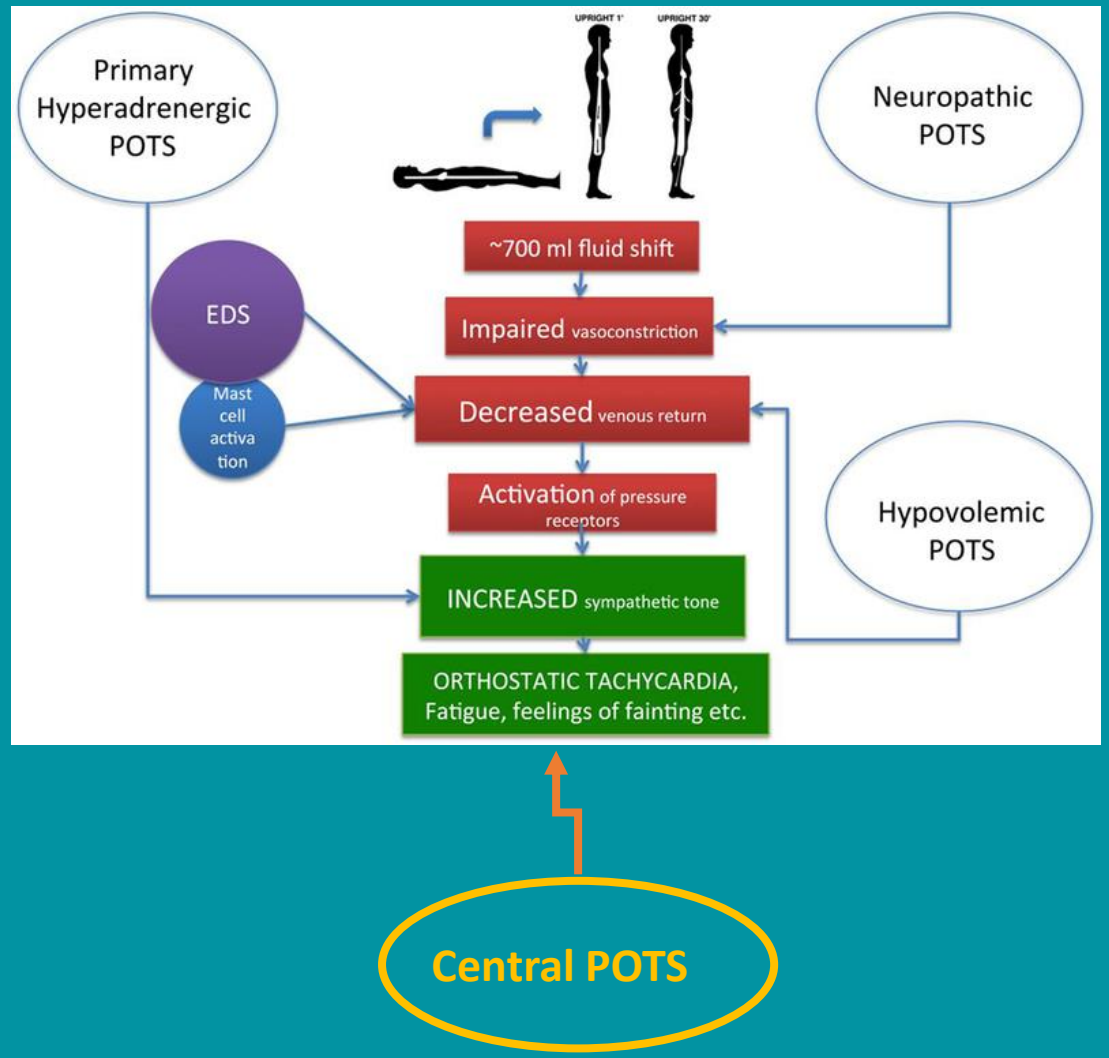
OH and POTS-Take Home message

- POTS is a form of orthostatic intolerance with a rapid increase in heartbeat.
- Most of POTS has a favorable prognosis when managed appropriately.
- Each case of POTS is different.

- POTS could be caused by (or mixed by)
  1. Peripheral denervation-Panautonomic neuropathy and could be an autoimmune condition.
  2. Reduced blood volume
  3. Overactivity of the sympathetic nervous system or Imbalance between sympathetic or para-sympathetic activity
  4. Central effect is not uncommon with similar symptoms of CBF hypoperfusion, HV and balance instability.
     - Good response to SSRI treatment
     - Higher Psychomotor score.
     - most typical young lady POTS

What is POTS?

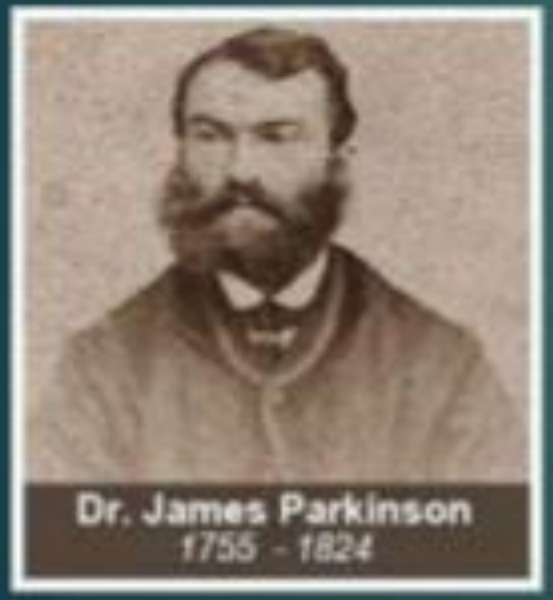
- **I. Neuropathic POTS**: could be immune-mediated
- **II. Hyperadrenergic POTS**: Overactivity of the sympathetic nervous system or Imbalance between sympathetic or para-sympathetic activity
- **III. Low blood volume POTS**: Reduced blood volume can lead to POTS.
- **IV. Central POTS (my classification)**:
  - Good response to SSRI treatment
  - Higher Psychomotor score.
  - most typical young lady POTS

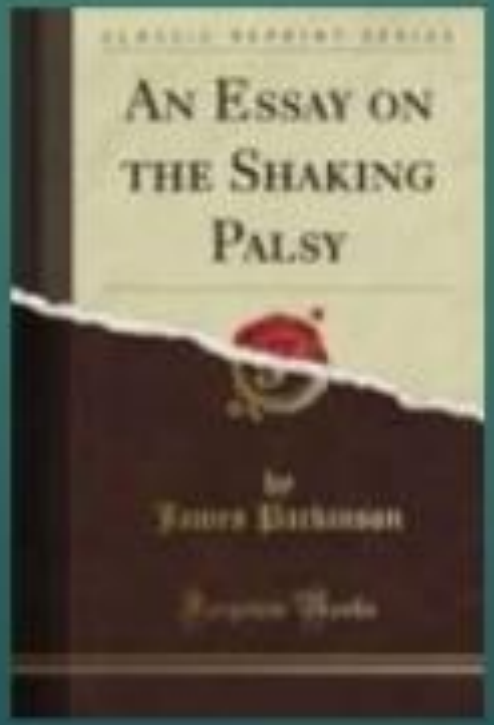


Parkinson's Disease

巴金氏症

- In 1817 a detailed medical essay was published on the subject by London doctor James Parkinson.
- Jean-Martin Charcot was the first to truly recognise the importance of Dr.Parkinson's work and renamed the disease which was formerly named *paralysis agitans* (shaking palsy) after him.





巴金森氏症的診斷

I am

Trapped.

I am

Trapped.

I am

Trapped.

I am

Trapped.

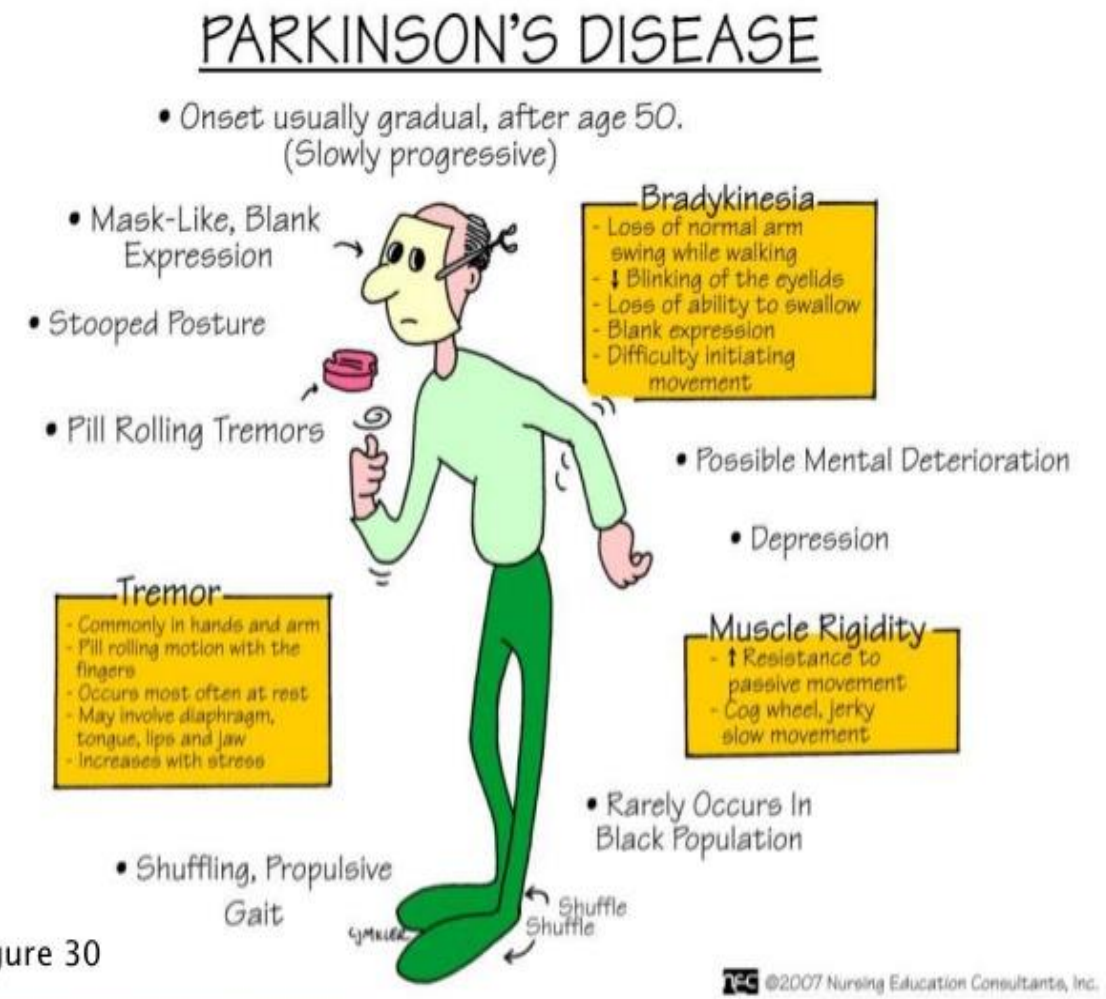
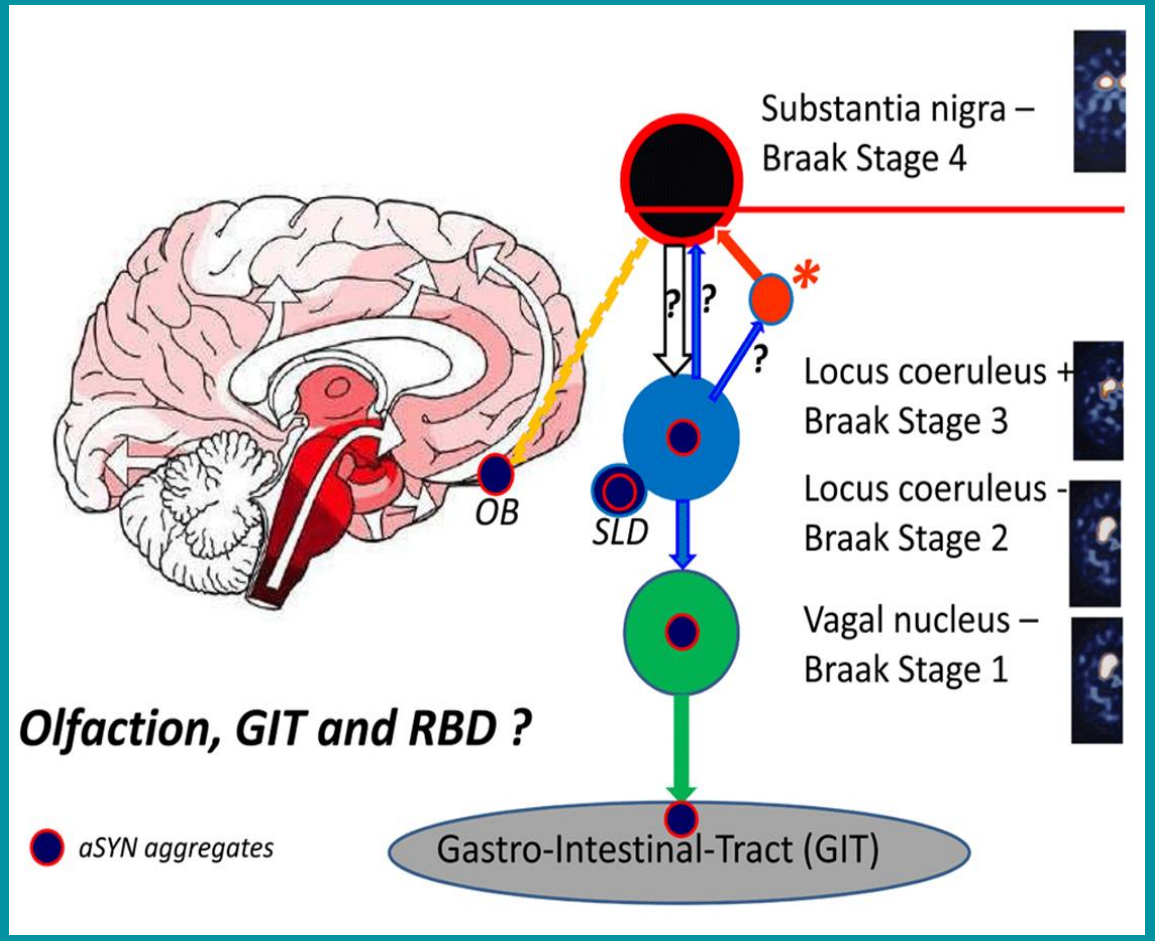


Figure 30

Pathophysiology Of Parkinson's Disease



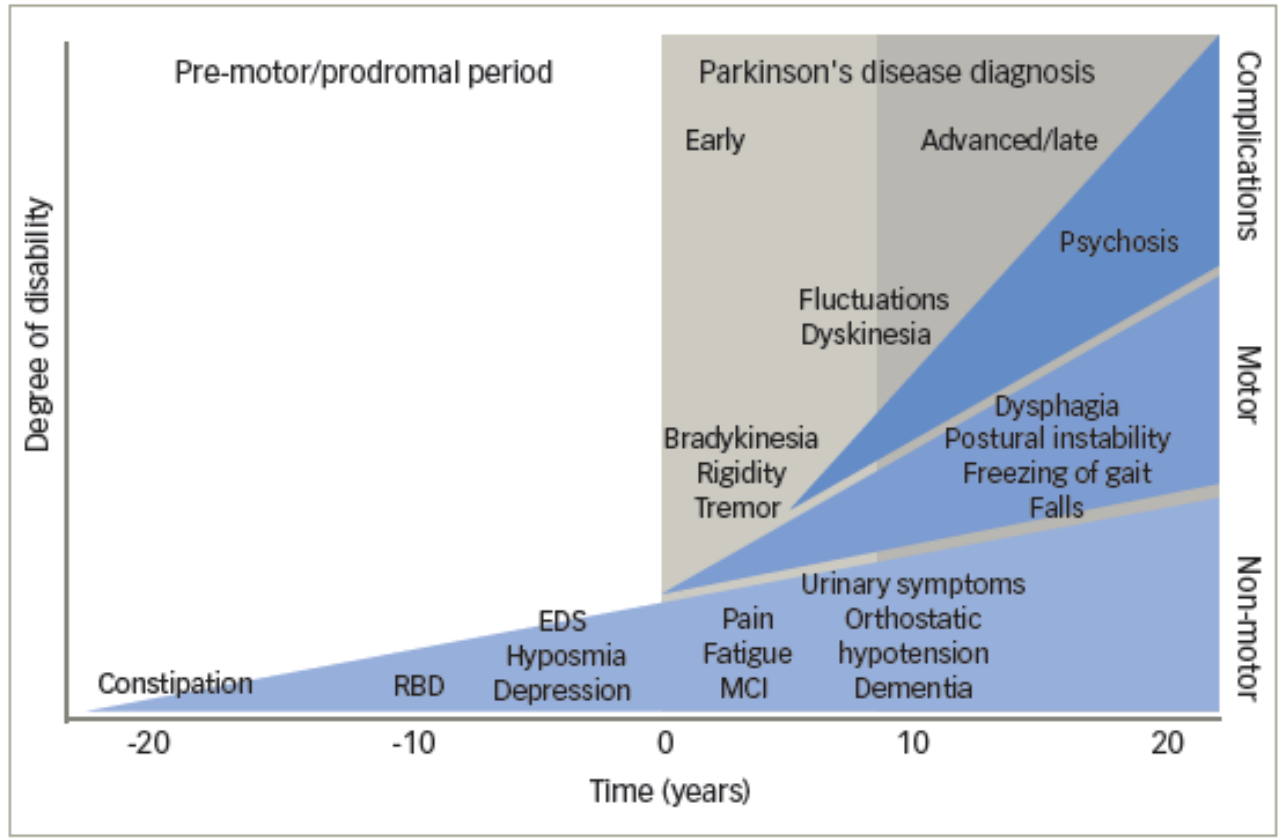
帕金森症大腦早期預警 科學家找到關鍵線索
BBC 20190622

英國科學家說，他們找到了大腦中導致帕金森症（Parkinson's disease）的早期訊號。這意味著在患者出現任何症狀前15-20年，大腦中就會呈現早期變化。
倫敦國王學院的研究人員說，這一發現可能會為帕金森症帶來新的篩查和治療手段

- 迄今為止，還沒有找到治癒帕金森症的方法。但有一些辦法可以幫助控制病情。
- 意味著什麼？該研究為能夠早期治療帕金森症提供了一線希望。因為帕金森症無藥可救，早期治療則是最佳機會

圖片版權KING'S COLLEGE LONDON Image caption大腦掃描圖像，左側為正常大腦，中間是還未出現症狀的大腦，右側為患病者大腦，從圖中可以看到藍/黑色部分的血清素在患病過程中逐漸減少。

Figure 1. Clinical symptoms and time course of Parkinson's disease[3]



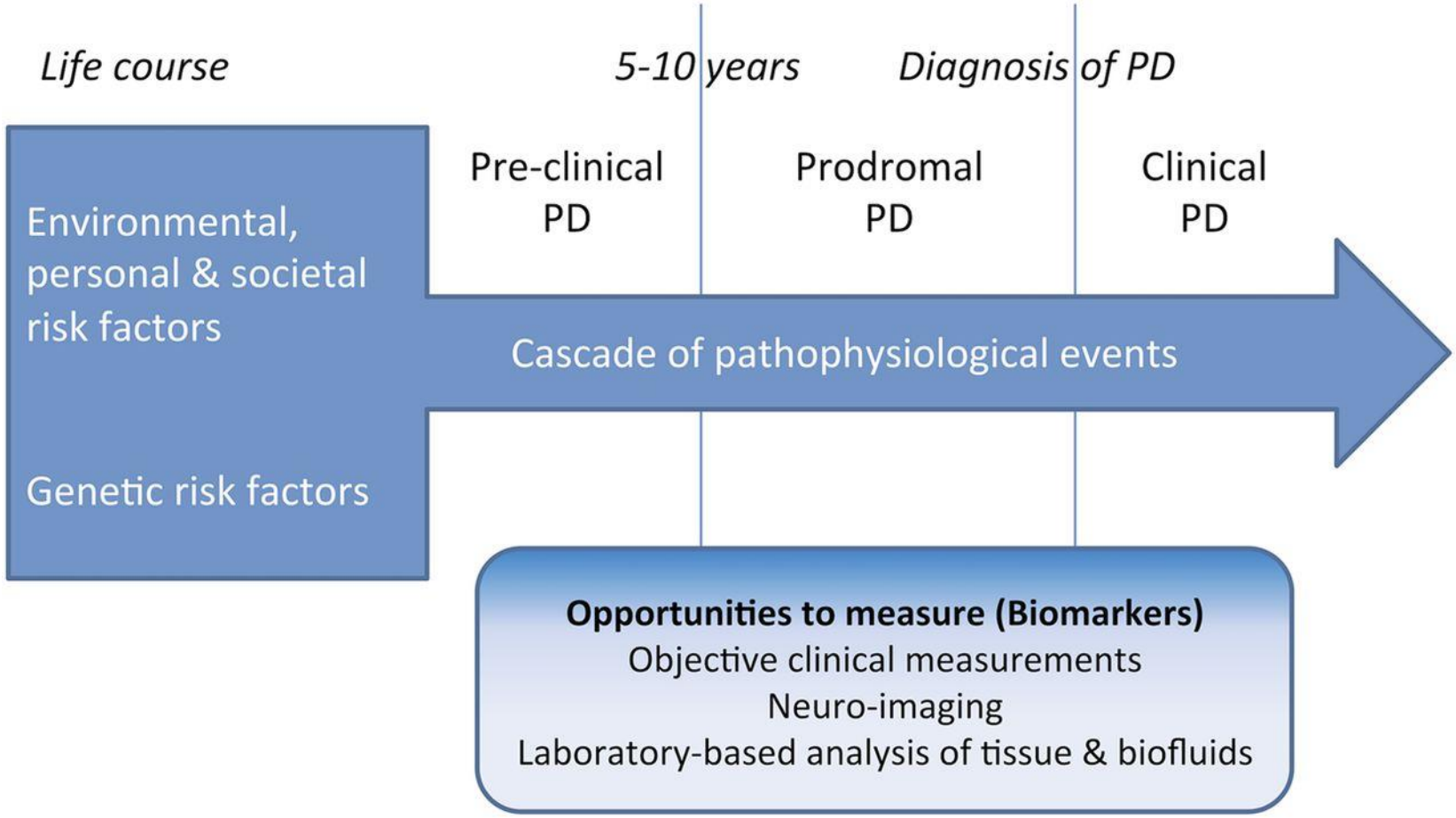
EDS = excessive daytime sleepiness; MCI = mild cognitive impairment; RBD = rapid eye movement sleep behavior disorder. Reproduced with permission from Kalia et al., 2015.[3]

病人説我才五十歲，怎麼可能退化，得這種病？
數据会説話：

PARKINSON'S DISEASE-Incidence

- Annual incidence 0.2/1000 & prevalence of 1.5/1000.
- Prevalence rates are similar throughout the world, except lower rates in China /West Africa.
- Affects 1% of those over 55 years, 1.5% of people 70-79 years of age
- Generally occurs between 50-80 years
- Sex incidence is about equal.

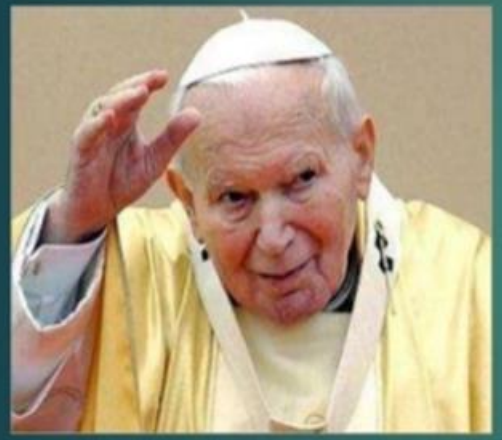
A schematic showing determinants of risk, the prediagnostic phase (preclinical and prodromal phases) and clinical phase of Parkinson's disease, along with the parallel application of risk and disease progression markers to measure disease activity across phases.



Alastair John Noyce et al. J Neurol Neurosurg Psychiatry 2016;87:871-878

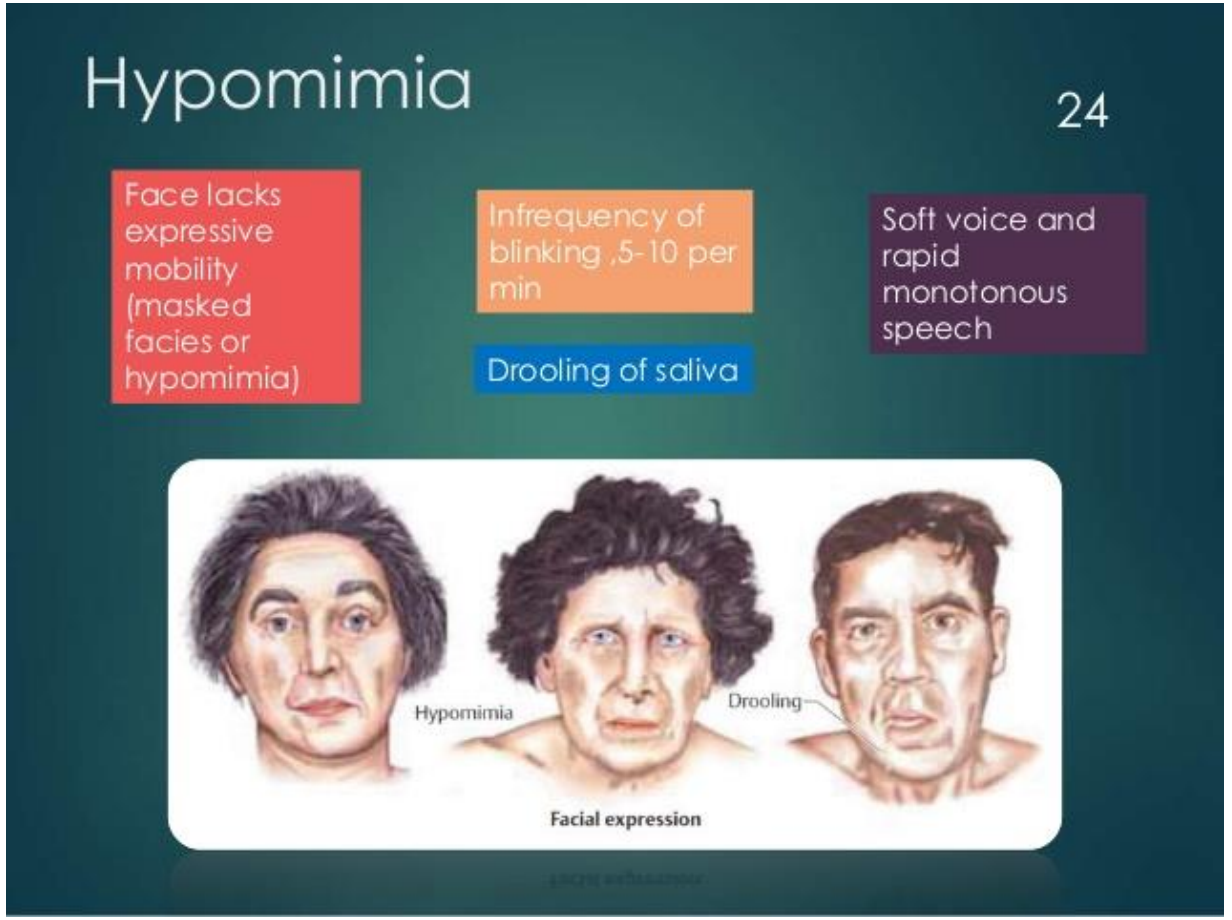
JNNP

Famous personalities



AI人臉辨識? AI医療診断?
提早診断、提早預防?

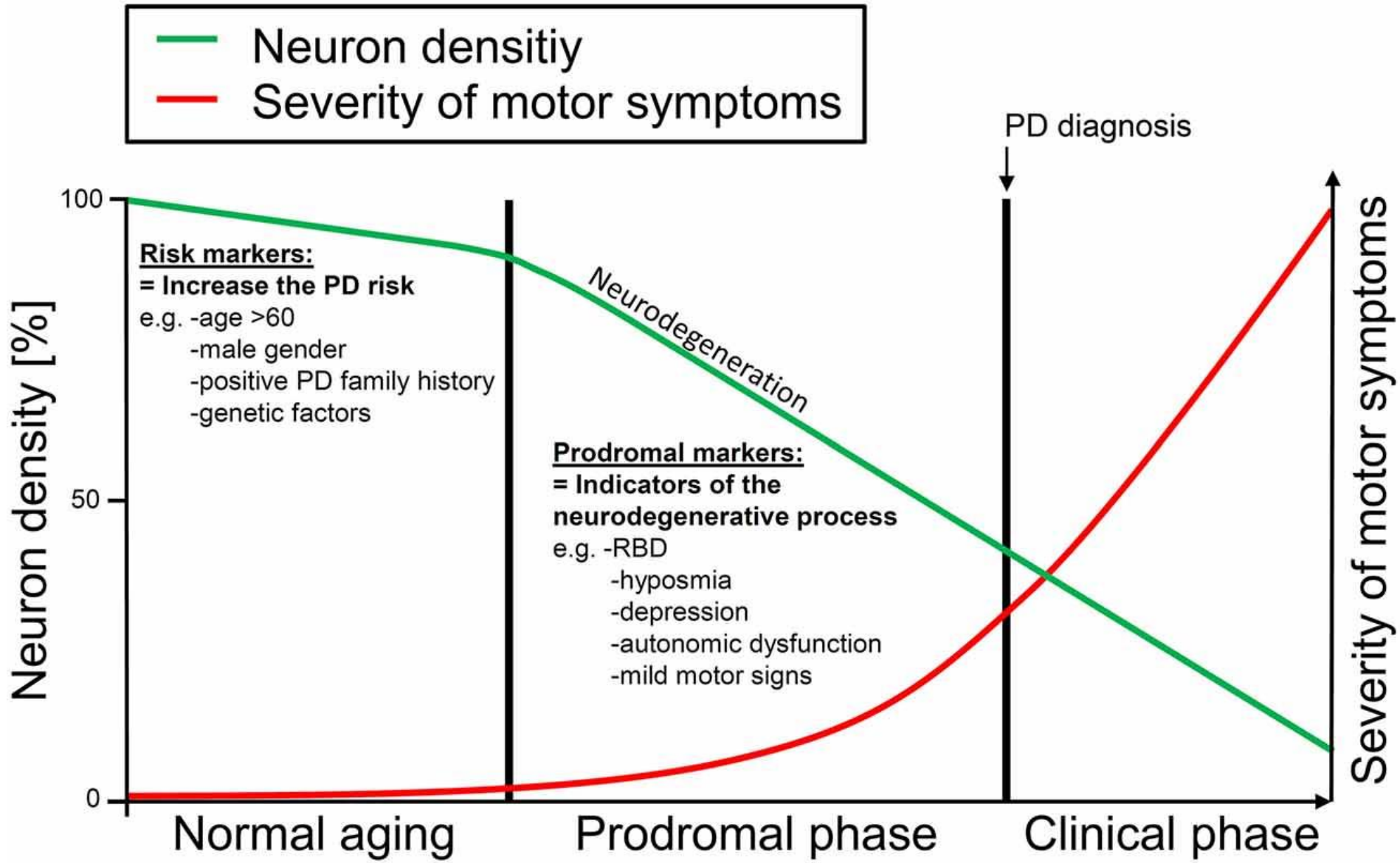
望聞问切



望而知之謂之神
聞而知之謂之聖
問而.....巧
切.....工

What are some of the non-motor symptoms of Parkinson’s?

Disturbances in the Sense of Smell	Sleep Problems	Depression and Anxiety	Pain	Psychosis
Fatigue	Cognitive Changes	Weight Loss	Gastrointestinal Issues	Lightheadedness
Urinary Issues	Sexual Concerns	Sweating	Melanoma	Personality Changes

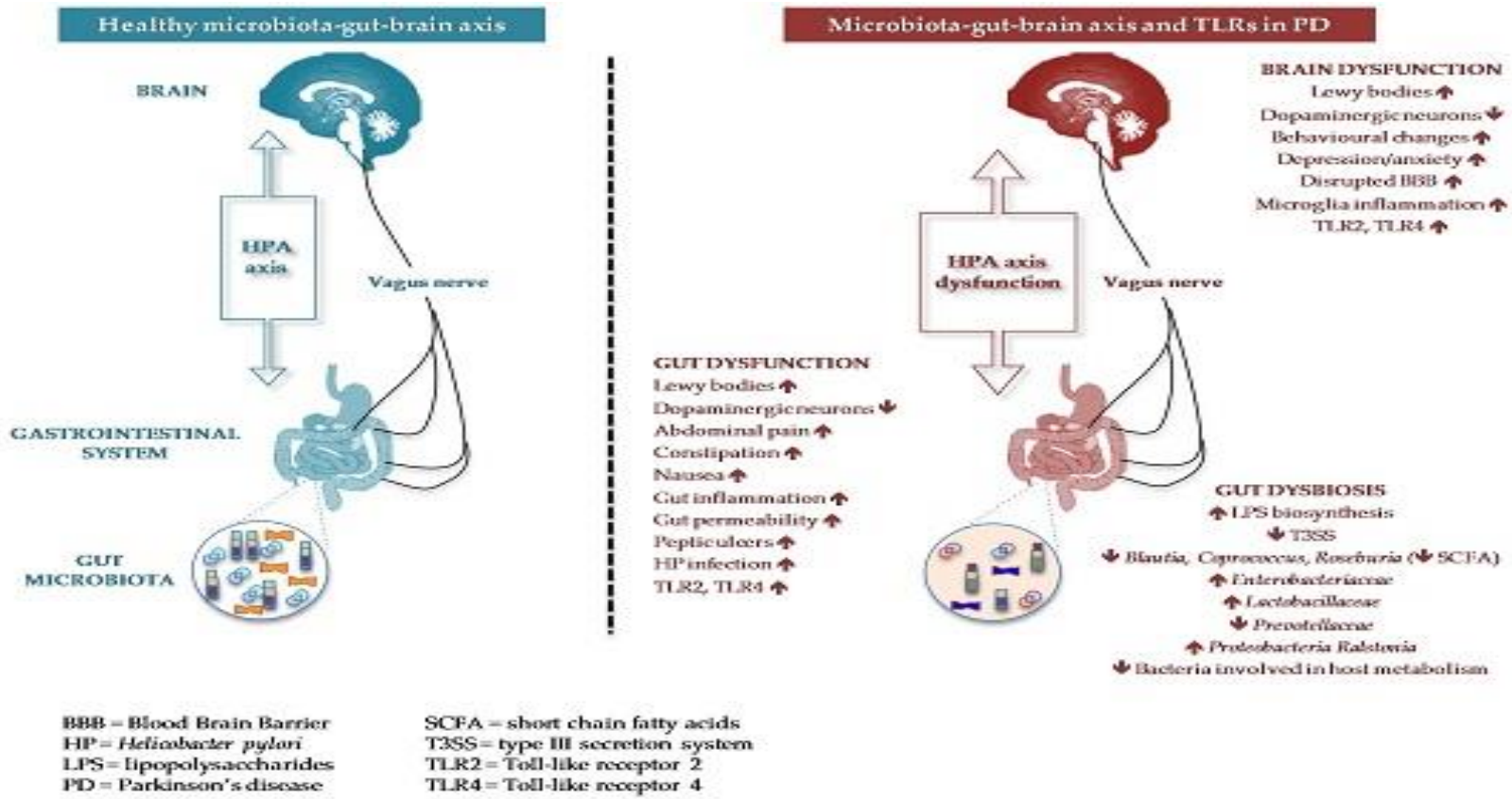

Neuron densitiy
Severity of motor symptoms
PD diagnosis
100
50
0
Neuron density [%]
Severity of motor symptoms
Risk markers:
= Increase the PD risk
e.g. -age >60
-male gender
-positive PD family history
-genetic factors
Neurodegeneration
Prodromal markers:
= Indicators of the neurodegenerative process
e.g. -RBD
-hyposmia
-depression
-autonomic dysfunction
-mild motor signs
Normal aging
Prodromal phase
Clinical phase

如何提早診斷巴金森氏症的策略
Strategies to diagnose prodromal PD

- **Combination of non-motor symptoms**
- **Presence of risk factors**
  - **Age**
  - **+ family History of PD**
- **Imaging markers: DAT SPECT, Cardiac scintigraphy, NMR**
- **Biochemical markers**

PD早期診斷、早期預防
露出曙光

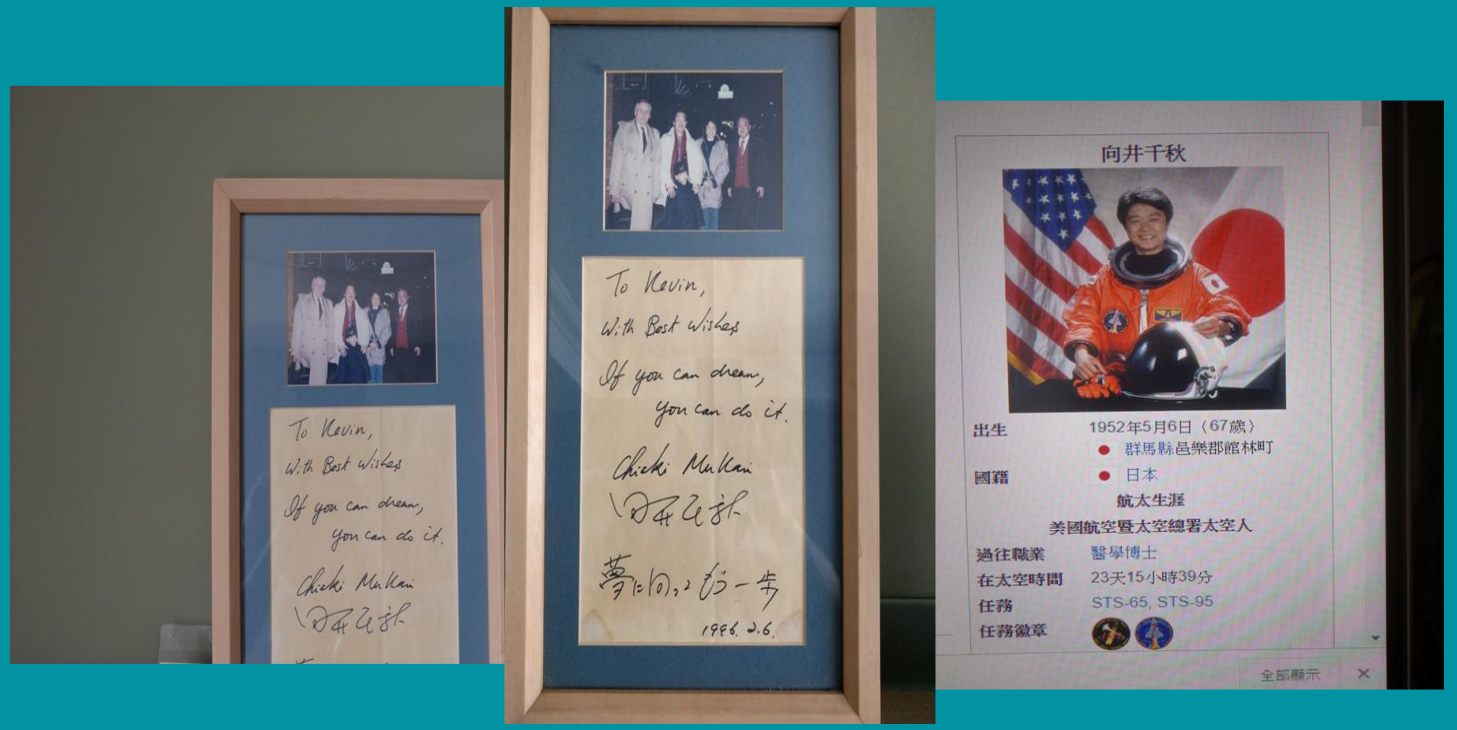
神經退化疾病腸通腦机轉-另契機



BBB = Blood Brain Barrier
HP = *Helicobacter pylori*
LPS = lipopolysaccharides
PD = Parkinson's disease
SCFA = short chain fatty acids
T3SS = type III secretion system
TLR2 = Toll-like receptor 2
TLR4 = Toll-like receptor 4

The Late Onset POTS in Prodromal Parkinson's disease

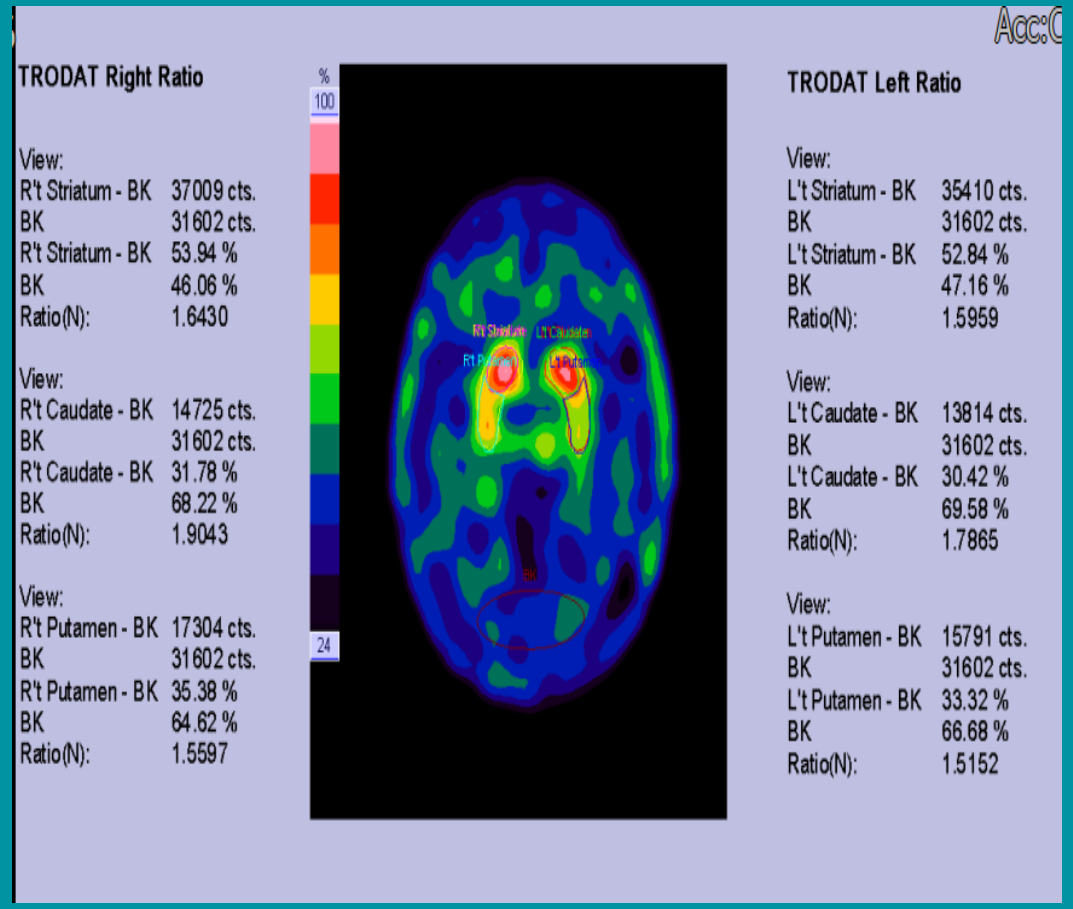
值得紀念的日子及照片



ISAN 2007 in Kyoto世界自律神經學會年會

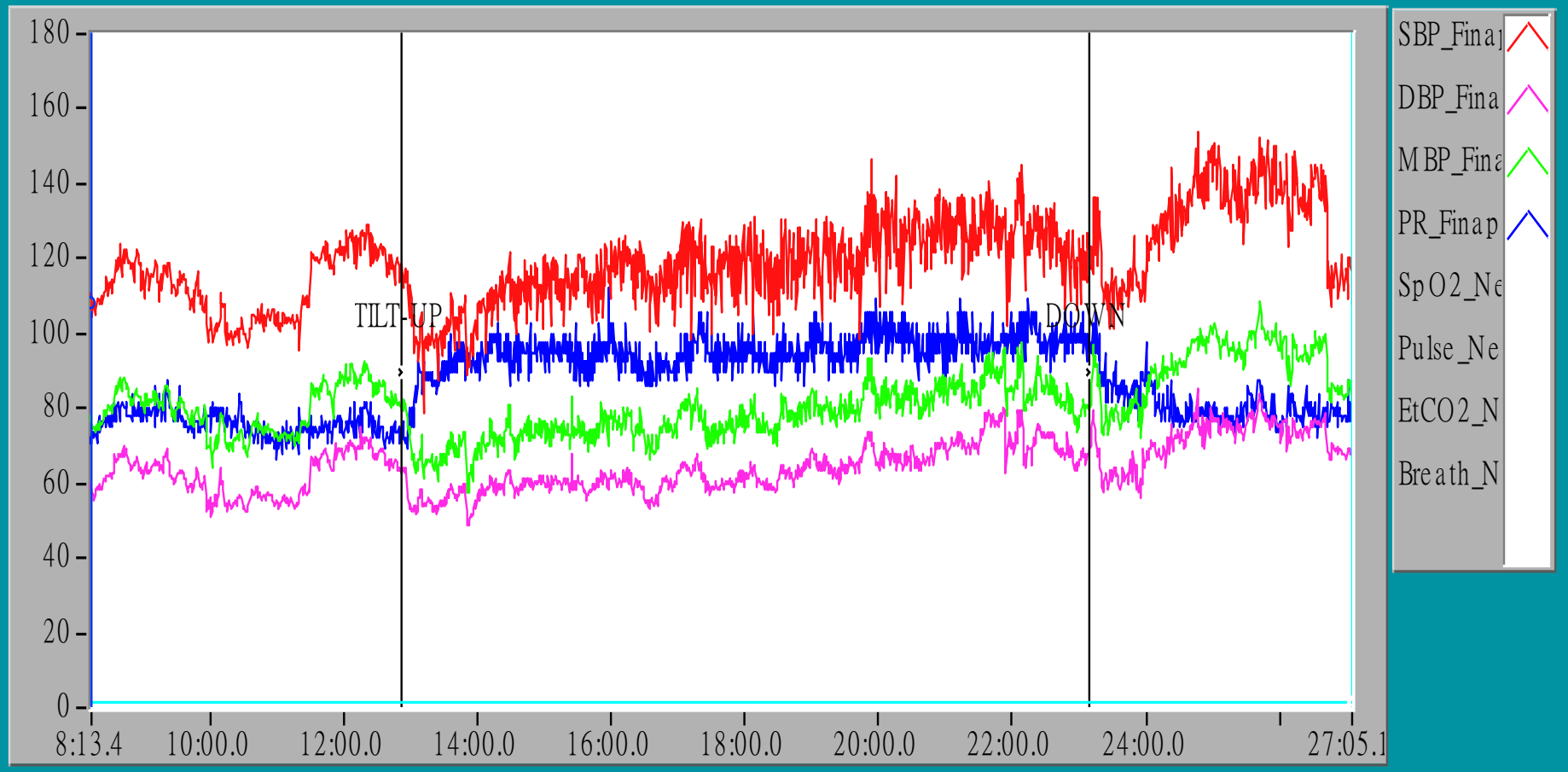
Early PD-POTS

- 6114714　劉0蘭 66 y/o (F)
- Hx: episodes of dizziness with dyspnea sometimes for several months; Insomnia with RBD(+)
- NE:
  - Mask(+),
  - Resting tremor=+/-
  - Rigidity=-/-
  - Bradykinesia(+-/+-)
  - Stooped posture (+-)
- Trodat=2,
- UPDRS=2,0,5,0
- DX= PD, H& Y stage 1



6114714　劉0蘭 66 y/o (F)

PD-TILTING TABLE TEST



6114714　劉0蘭 66 y/o (F)

Our clinical data: from PPD to PD cases in recent 5 years
105.05 ~109.08

姓名	病歷號	年齡	性別	看診日期	確診日期	TRODAT					備註
						1st DATE	SCALE	2nd DATE	SCALE	進步	
陳　　華	1227975	75	F	1060327	106/11	1060328	0-1				typical PD
林	5972347	72	F	1050320	106/06	1050324	0-1				R't hand tremor now
黃	547382	70	F	1050818	106/07	1050823	0-1	1070524	1		Start to have L't hand tremor
陳	5085951	50	F	1060620	106/09/13	1060627	1				R't tremor now
詹　　娥	1422001	69	F	106/0611	106/09/14	1060615	1				R't LL tremor now
林	1092213	57	F	1060915	107/03/01	1060915	1				BEGIN HAND TREMOR ,STAGE I
廖　　華	5509719	73	F	1060422	107/0723	1060428	2				R't hand tremor
林	768283	65	F	10202	105/05/15	1050513	1-2	1060721	1	v	(10202 Dx:PPD)
施	1134230	67	F	1070103	108/01/07	1070125	2				PD STAGE I
劉	6114714	66	F	1070925	108/01/22	1070926	2				PD early
李	5237449	57	F	1071104	108/01	10711	0-1				HAND TREMOR DURING TAKING MEALS
潘　　絨	5619842	78	F	106/08?	1090820?	1090826	0/0				PPD

Demography and Lab. Data in PPD with or without POTS
(primitive data)

	PPD with POTS	PPD
N(M:F)	12 (6:6)	23(7:16)
Age**	50.9	63
RAM	10.3	10.1
AR TEST		
SSR-Palms	2.07	1.35
SSR-Soles**	1.03	0.32
VM	1.6	1.4
DB	13	11
POTS(HR)**	31	14

** P <0.01

	PPD with POTS	PPD
N	12	23
SSR-Palms	4(33.3%)	15(65.2%)
SSR-Soles**	7(58.3%)	22(95.6%)
Trodat	8(66.6%)	15(65.2%)
RBD*	3(60%) n=5	6(33.3) n=18
Tapping**	4(33.3%)	18(61%)

** P <0.01 * P <0.05

老化可以
改變嗎？

神經退化
疾病可以
改變嗎？

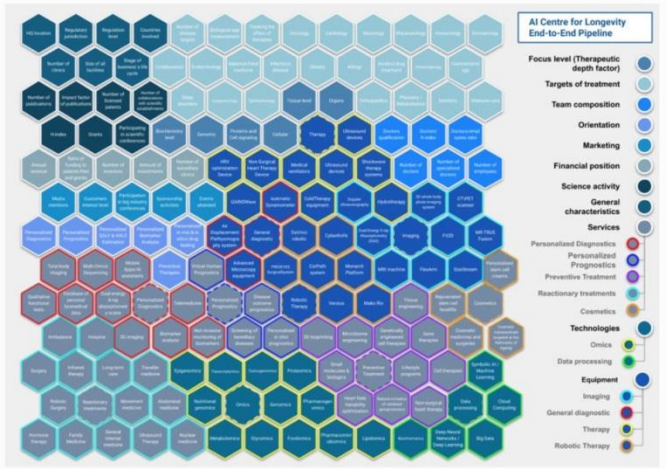
老化可以
改變嗎？

老化可以
改變嗎？

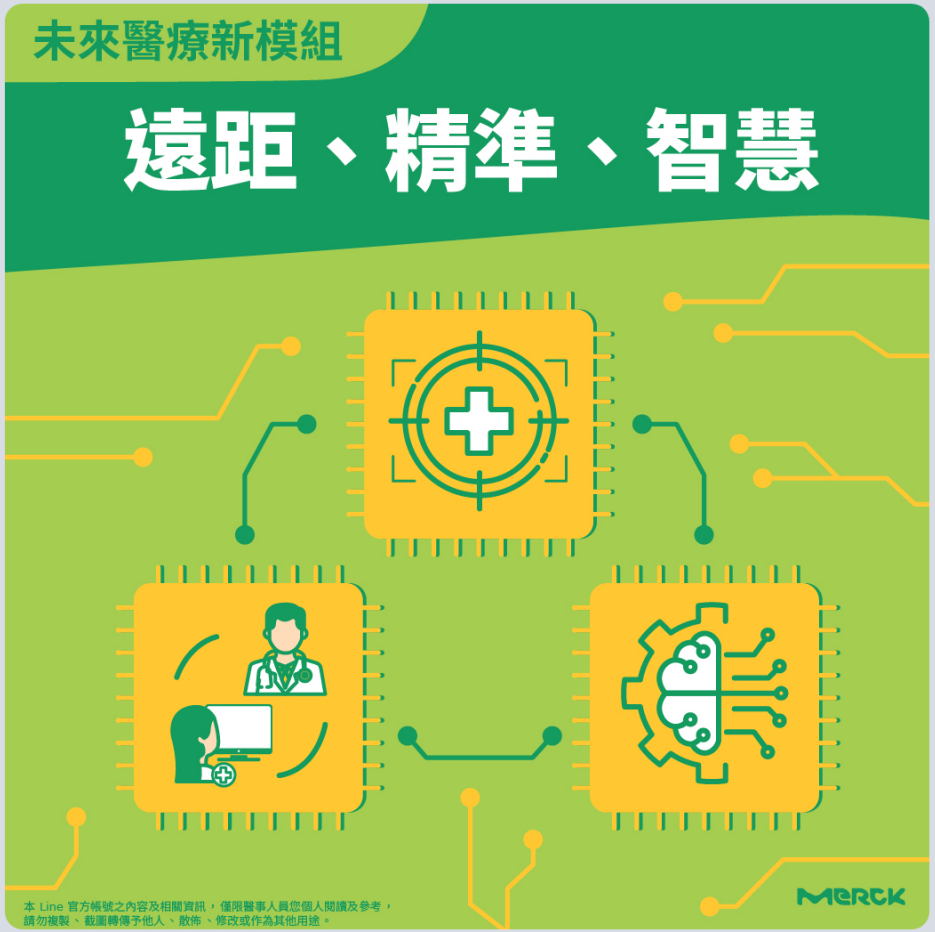
Forbes

Leveraging AI To Accelerate Precision Health For Longevity

Margaretta Colangelo Former Contributor
COGNITIVE WORLD Contributor Group
AI



AI Center For Longevity End-to-End Pipeline.... [+]
AGING ANALYTICS AGENCY


未來醫療新模組
遠距、精準、智慧
本 Line 官方帳號之內容及相關資訊，僅限醫事人員您個人閱讀及參考，
請勿複製、截圖轉傳予他人、散佈、修改或作為其他用途。
MERCK

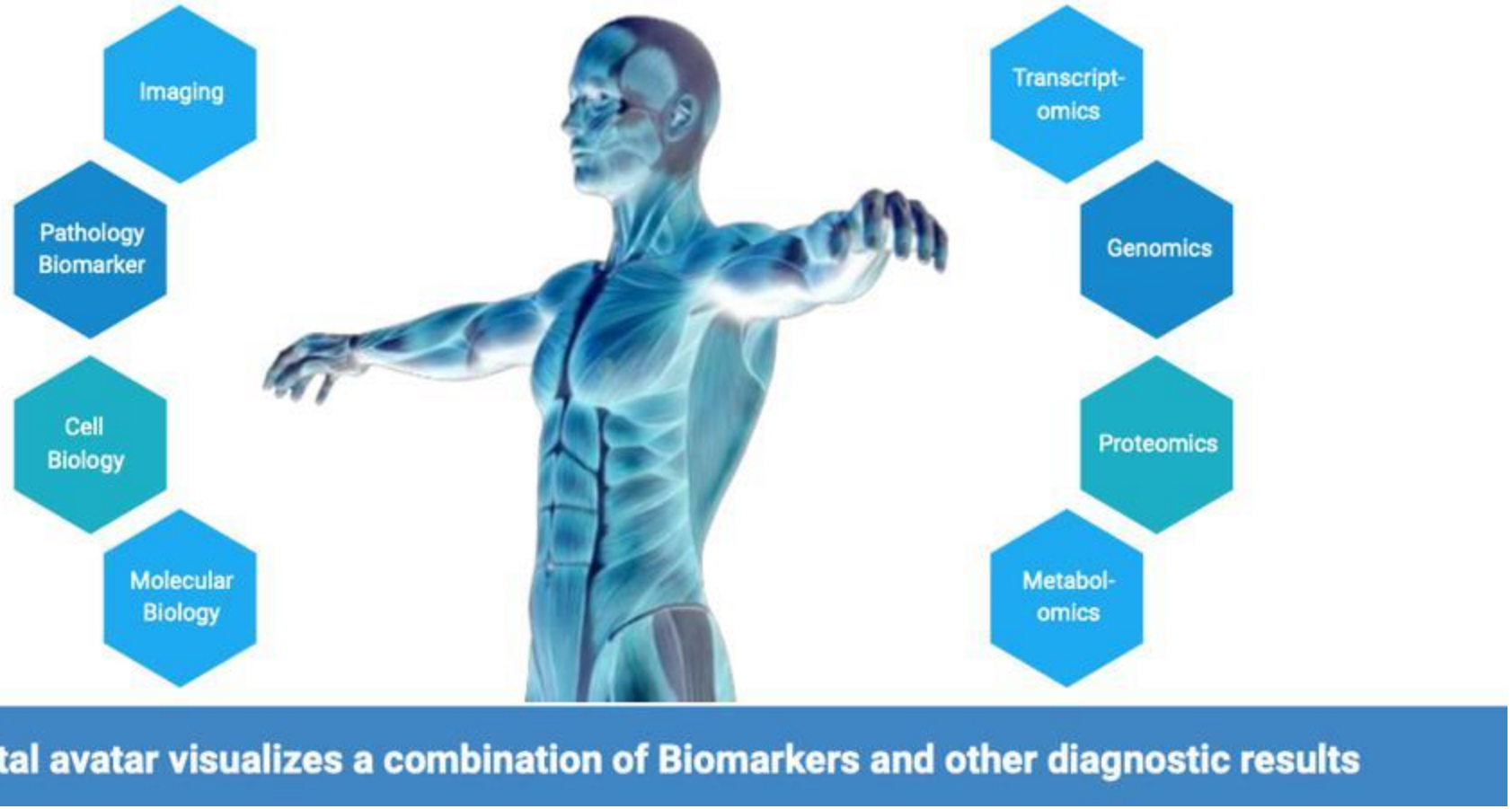
下午3:35


AI 加速抗老精準健康管理
(precision health for longevity)
MERCK

下午3:33

Minimum Required Biomarkers List

1. Gait (Walking) Speed
2. Timed Get Up and Go
3. Chair Rising
4. Grip Strength
5. Standing Balance
6. Purdue Pegboard Test
7. Spirometry: Forced Expiratory Volume in 1 Second (FEV1)
8. Bone Density, Bone Mass Hip: Dual X Ray Absorptiometry for Bone Health
9. Broadband Ultrasound Attenuation (BUA) at Heel for Bone Health
10. Computed Tomography for Bone Health
11. Dual X Ray Absorptiometry for Estimated Leg Muscle Mass
12. Bioelectrical Impedance Analysis for Muscle Mass
13. Computed Tomography for Muscle Mass
14. Magnetic Resonance Imaging for Muscle Mass
15. Body Potassium for Muscle Mass
16. Abdominal Fat; Waist Circumference
17. Body Mass; Body Mass Index; Body Weight
18. Blood Pressure; Sphygmomanometry
19. Standard Lipid Profile: Total Cholesterol; LDL-C; HDL-C; Triglycerides
20. Glycated haemoglobin (HbA1C)
21. Fasting Plasma Glucose
22. Verbal Fluency
23. Digit-Symbol Coding
24. Digit Span Backward
25. Boston Naming Test
26. Stroop Task
27. Block Design Test
28. Raven's Progressive Matrices
29. Rey Auditory Verbal Learning Test
30. Benton Visual Retention Test
31. Adiponectin
32. DHEAS:Cortisol Ratio
33. DHEAS
34. Growth Hormone; IGF-1
35. Leptin
36. Ghrelin
37. Melatonin
38. Estrogens
39. Somatostatin
40. Testosterone
41. Thyroid Hormones
42. C-Reactive Protein
43. Neutrophils



Digital avatar visualizes a combination of Biomarkers and other diagnostic results

Comparisons of the Nonlinear Relationship of Cerebral Blood Flow Response and Cerebral Vasomotor Reactivity to Carbon Dioxide under Hyperventilation between Postural Orthostatic Tachycardia Syndrome Patients and Healthy Subjects

Shyan-Lung Lin 1,* , Shoou-Jeng Yeh 2, Ching-Kun Chen 1, Yu-Liang Hsu 1 , Chih-En Kuo 1 ,Wei-Yu Chen 1 and Cheng-Pu Hsieh 1

Abstract: Postural orthostatic tachycardia syndrome (POTS) typically occurs in youths, and early accurate POTS diagnosis is challenging. A recent hypothesis suggests that upright cognitive impairment in POTS occurs because reduced cerebral blood flow velocity (CBFV) and cerebrovascular response to carbon dioxide (CO2) are nonlinear during transient changes in end-tidal CO2 (PETCO2).
This novel study aimed to reveal the interaction between cerebral autoregulation and ventilatory control in POTS patients by using tilt table and hyperventilation to alter the CO2 tension between 10 and 30 mmHg. The cerebral blood flow velocity (CBFV), partial pressure of end-tidal carbon dioxide (PETCO2), and other cardiopulmonary signals were recorded for POTS patients and two healthy groups including those aged >45 years (Healthy-Elder) and aged <45 years (Healthy-Youth) throughout the experiment. Two nonlinear regression functions, Models I and II, were applied to evaluate their CBFV-PETCO2 relationship and cerebral vasomotor reactivity (CVMR). Among the estimated parameters, the curve-fitting Model I for CBFV and CVMR responses to CO2 for POTS patients demonstrated an observable dissimilarity in CBFVmax (p = 0.011), mid-PETCO2 (p = 0.013), and PETCO2 range (p = 0.023) compared with those of Healthy-Youth and in CBFVmax (p = 0.015) and CVMRmax compared with those of Healthy-Elder. With curve-fitting Model II for POTS patients, the fit parameters of curvilinear (p = 0.036) and PETCO2 level (p = 0.033) displayed significant difference in comparison with Healthy-Youth parameters; range of change (p = 0.042), PETCO2 level, and CBFVmax also displayed a significant difference in comparison with Healthy-Elder parameters. The results of this study contribute toward developing an early accurate diagnosis of impaired CBFV responses to CO2 for POTS patients.

Keywords: POTS; cerebral blood flow; carbon dioxide; hyperventilation; cerebral vasomotor reactivity

J. Clin. Med. 2020, *9*, 4088 ;doi:10.3390/jcm9124088

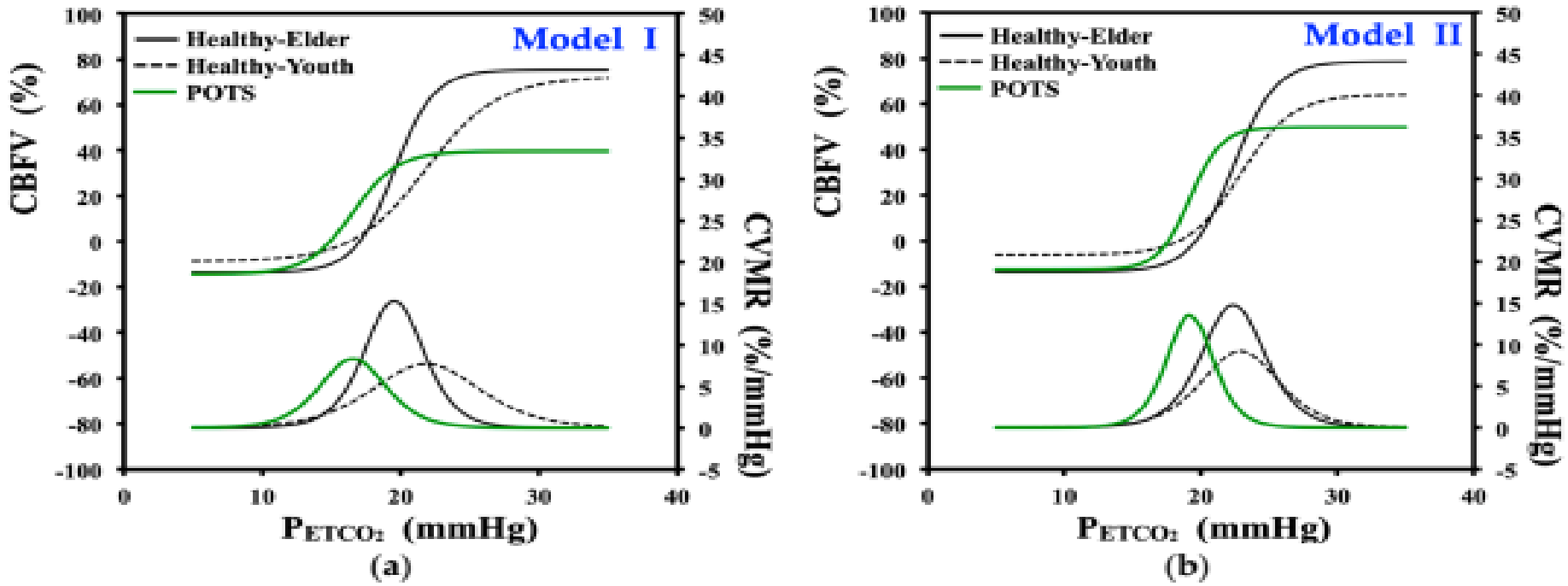


Figure 7. Nonlinear curve fit results of percentage change in CBFV responses to CO_2 (P_{ETCO_2}) during hyperventilation for the three subject groups: (**a**) nonlinear regression with curve-fitting Model I of Equation (2); (**b**) nonlinear regression with Model II of Equation (3).

J. Clin. Med. 2020, *9*, 4088 ;doi:10.3390/jcm9124088

Precision Medicine

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75%

Current untargeted drugs are ineffective in around three-quarters of all cancer patients.[1]

$1000

In 2003, it cost $54 million to sequence one human genome. Twelve years later, it cost around $1,000.[1]

190MN

In 2016, 28.3 million wearable devices were on the market but this will rise to ~190 million by 2022.[8]

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MULTIPLEX BIOMARKERS

Making use of increasingly powerful, multi-dimensional datasets will come from integrating multiple types of 'omics data and other biomarkers – leading to complex new tests that can make sense of multiple measurements to guide precision medicine.

LIQUID BIOPSIES

For diseases like cancer, getting hold of samples for testing biomarkers can involve invasive surgical procedures. So developing non-invasive 'liquid biopsy' tests, based on body fluids such as blood or urine, are set to change how diseases are diagnosed and treated in the future.

Not only are they simpler and less-inv for patients, they also give doctors the opportunity to get results more rapidly and

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BIOSENSORS AND INTERFACES

There is also a wealth of opportunities offered from integrating electronics with the human body which can sense changes in our biochemistry, through the development of innovative new biosensors[6] and interfaces. [7]

One well-known biosensor is already used for blood glucose testing by millions of diabetics around the world. However, although blood is often the gold-standard body fluid, samples can be painful to collect. Scientists are developing a new range of wearable sensors that can make meaningful measurements from other biological fluids - such as sweat, breath, saliva or eye fluids.

The study of biological interfaces is one of the most innovative and expanding a science and technology, as many medical devices and materials could be vastly

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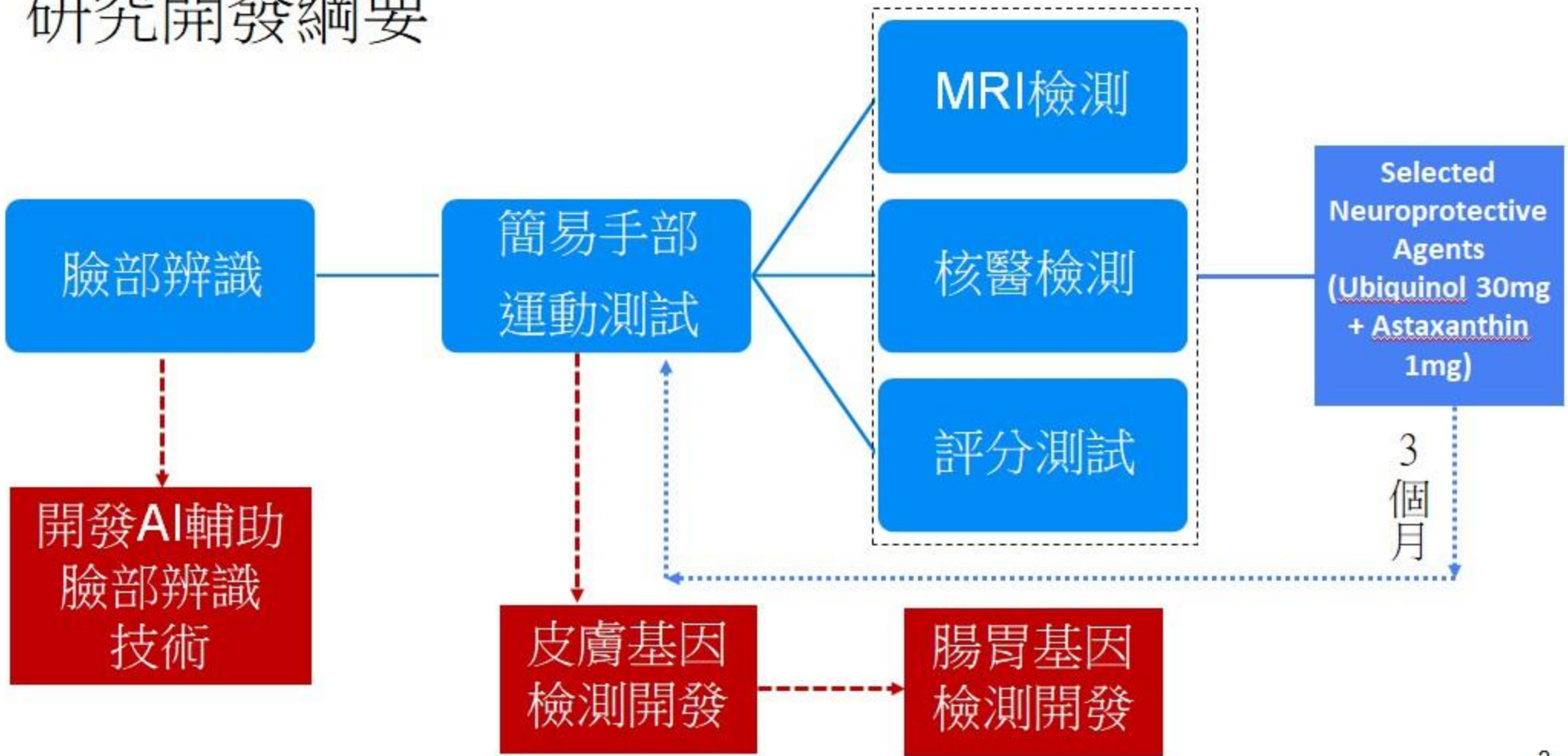
DIGITAL BIOMARKERS

The boom in fitness and wellness devices, such as fitness bands and smartwatches, provides access to an information base with huge opportunities for expansion to encompass disease monitoring or diagnosis. A staggering 28.3 million wearable devices made it to the market in 2016 and this is forecasted to rise to 189.9 million by 2022. [8]

Integrating consumer digital technologies with data collected from new biosensors will enable scientists to collect and track real-time physiological and behavioural data at scale. Analysing these huge datasets with the help of AI and machine learning will lead to new insights that can make accurate diagnoses about a person's current and future health - and recommend personalised interventions that will prevent or dela onset of disease.

巴金森氏症(Parkinson's Disease)早期發現與延緩發生研究開發綱要



A Journey to Autonomic and Vestibular Neuroscience

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Thank you for your Attention