



**HAND ARM
VIBRATION**

Biomarkers in Patients with Hand-Arm Vibration Injury Entailing Raynaud's Phenomenon and Cold Sensitivity, Compared to Referents

International conference

6-9 JUNE 2023

Espace Prouvé,
Nancy, France



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Aim

To investigate serum levels of biomarkers indicating inflammation, vascular or neural injury

- I. In Patients with hand-arm vibration injury compared to Referents
- II. In Patients with hand-arm vibration injury with Raynaud's Phenomenon (RP) compared to Patients without RP
- III. In Patients without RP, with and without increased cold sensitivity

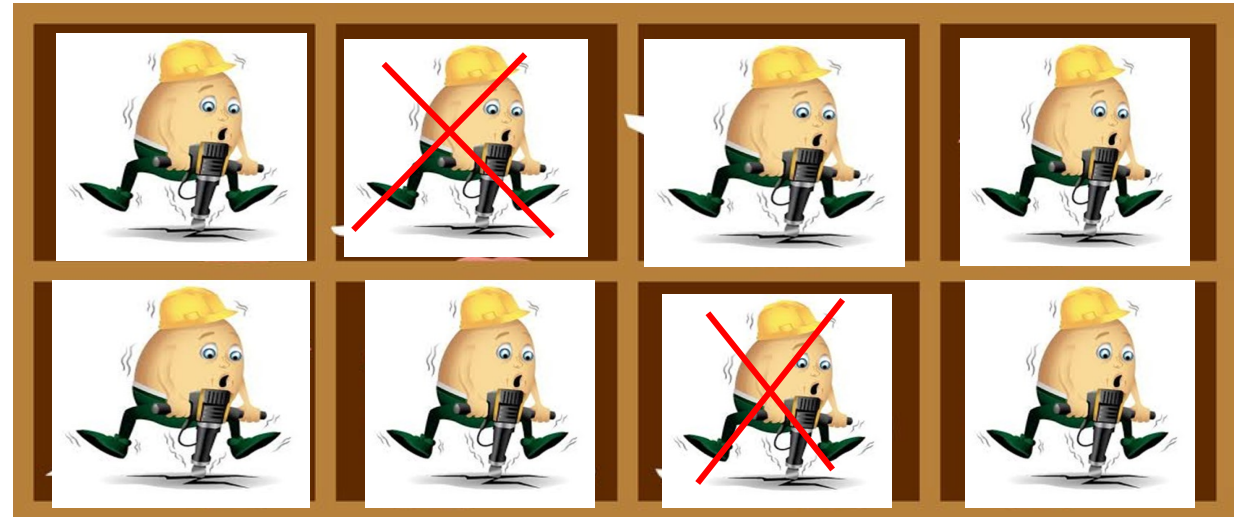


Background – Why biomarkers?

DIAGNOSIS
GRADING
PROGNOSIS



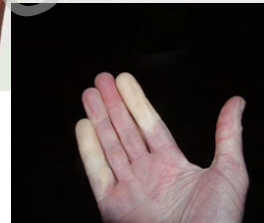
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DIAGNOSIS

- I. Typical symptoms and clinical findings...
- II. Sufficient and time related exposure...
- III. Differential diagnoses excluded...

Tingling
Numbness
Pain
Increased cold sensitivity/cold intolerance



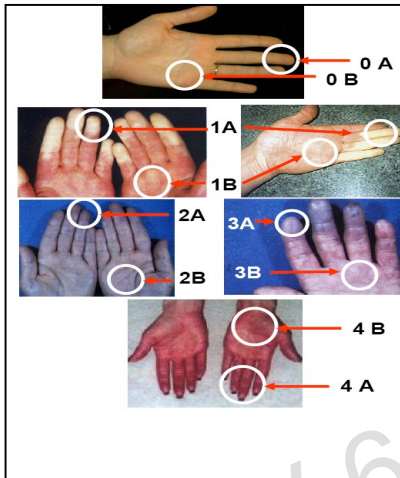
Impaired perception of touch
Impaired perception of cold
Impaired perception of warmth
Impaired dexterity

Episodes of finger blanching



DIAGNOSIS

- I. Typical symptoms and clinical findings...
- II. Sufficient and time related exposure...
- III. Differential diagnoses excluded...



Colour chart

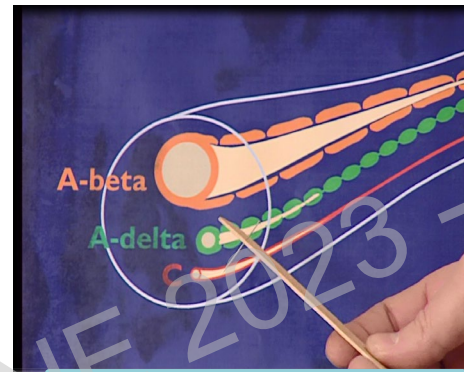
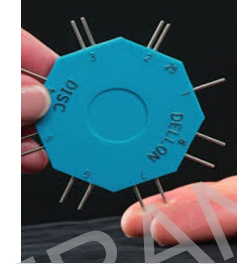
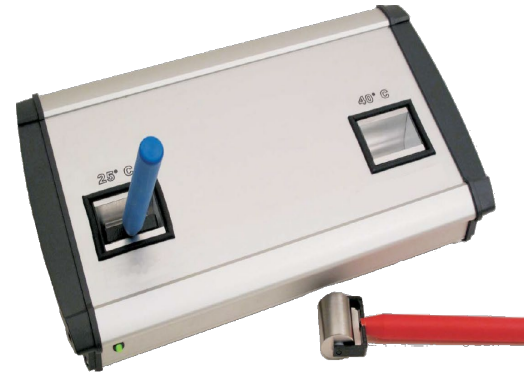


Photo of worst episode of finger blanching



Cold provocation test

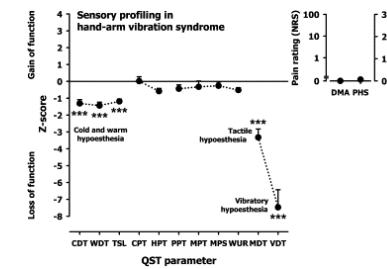
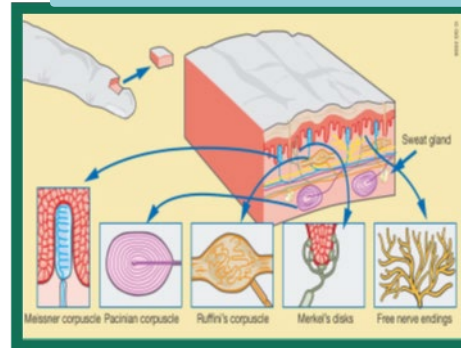
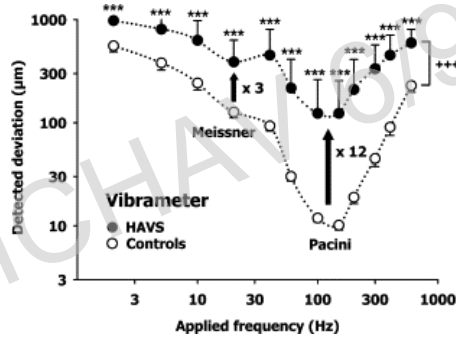




Vibrotactile Quantitative Sensory Testing

Neurosensory unit

Thermal Quantitative Sensory Testing



Electrophysiology

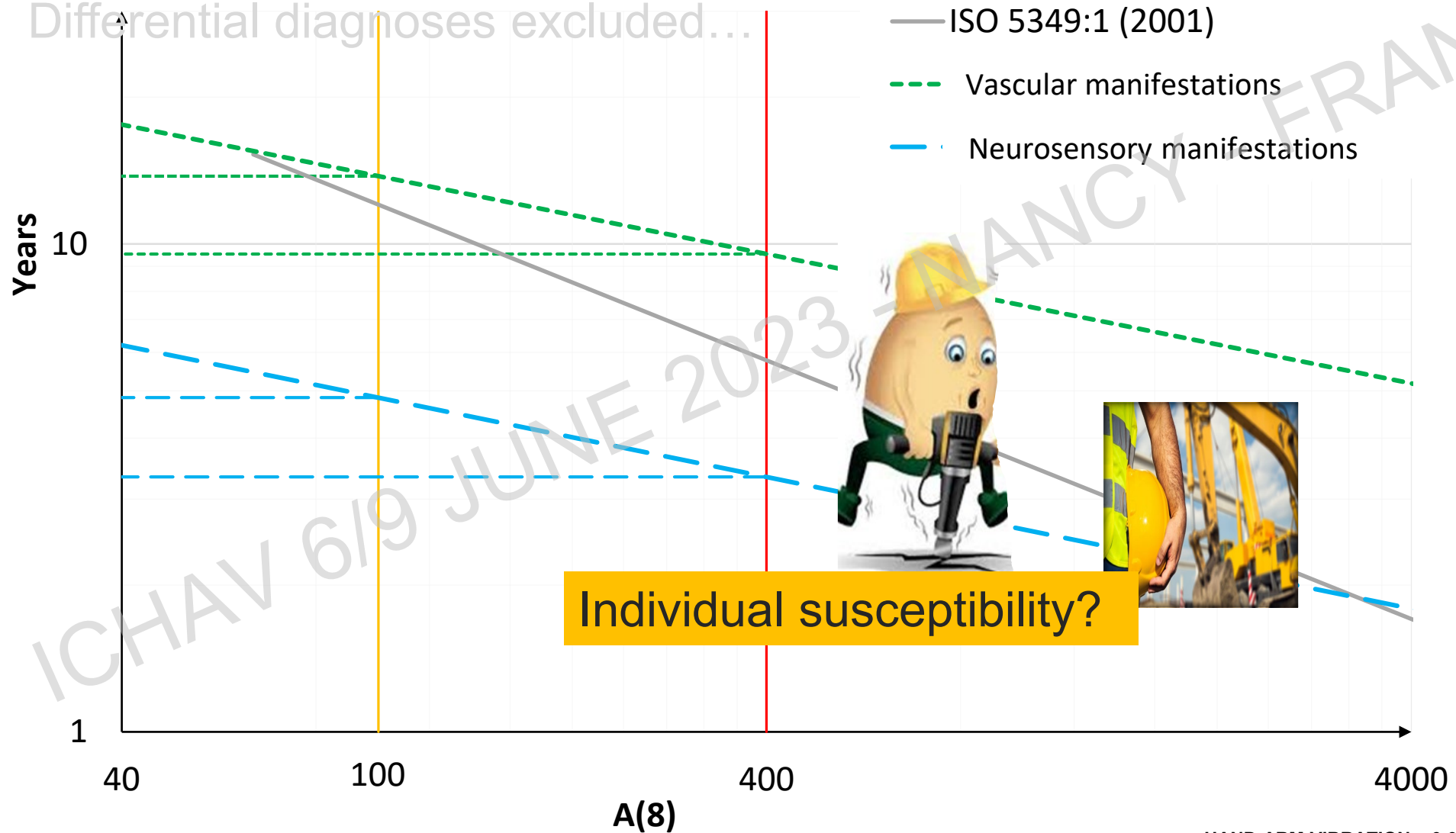
Rolke R et al., Hand-arm vibration syndrome: clinical characteristics, conventional electrophysiology and quantitative sensory testing. Clin Neurophysiol. 2013 Aug;124(8):1680-8.

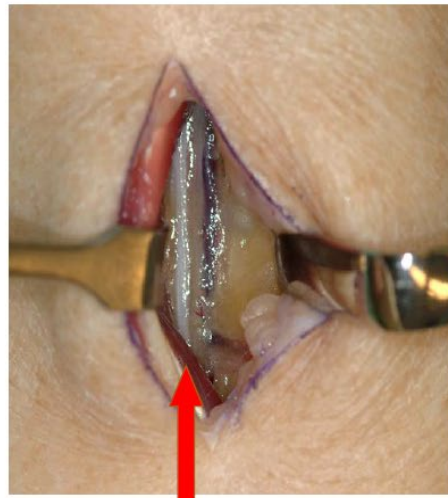
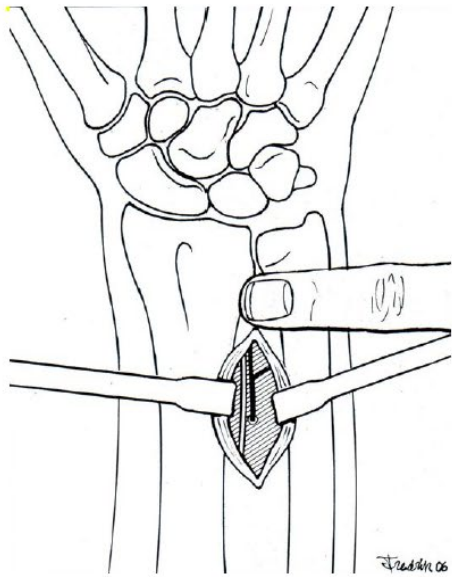
DIAGNOSIS

Typical symptoms and clinical findings...

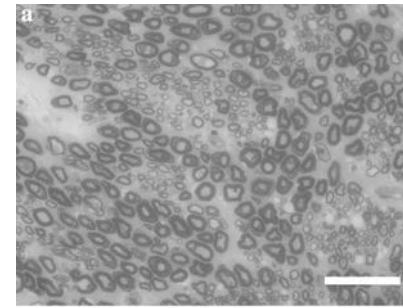
I. Sufficient and time related exposure...

II. Differential diagnoses excluded...

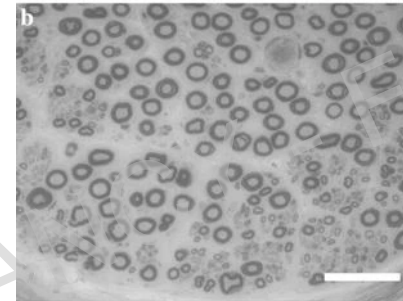




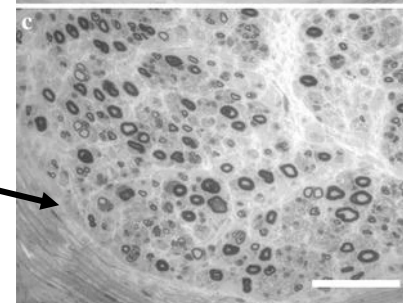
Posterior interosseus nerve



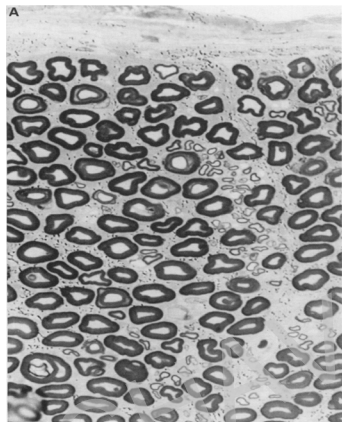
a) control subject without CTS



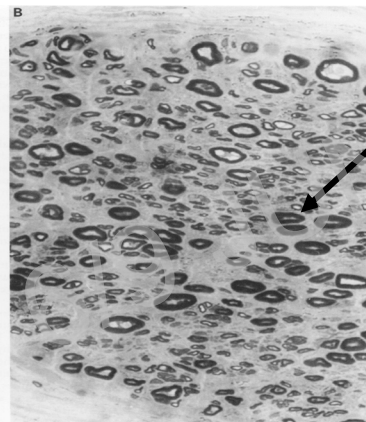
b) Non-diabetic patient with CTS



c) Diabetic patient with CTS



Normal nerve



Exposed to vibration

Reduced number of myelinated nerves

Thomsen, N.O.B. et al. Reduced myelinated nerve fibre and endoneurial capillary densities in the forearm of diabetic and non-diabetic patients with carpal tunnel syndrome. *Acta Neuropathol* 118, 785–791 (2009).

Stromberget al. Structural nerve changes at wrist level in workers exposed to vibration. Occupational and Environmental Medicine 1997;54:307-31 13

DIAGNOSIS

- I. Typical symptoms and clinical findings...
- II. Sufficient and time related exposure...
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Table 1. Secondary causes of Raynaud's phenomenon. Reproduced from Devgire V, Hughes M. Raynaud's phenomenon. *Br J Hosp Med (Lond)* 2019;80:658–64.

Vascular (usually proximal large vessel disease, often unilateral symptoms)	Compressive (eg cervical rib) Obstructive: non-inflammatory (ie atherosclerosis); inflammatory vascular disease (eg thromboangiitis obliterans (Buerger's disease))
Occupational	Hand–arm-vibration syndrome (vibration white finger)
Autoimmune conditions	Systemic sclerosis Systemic lupus erythematosus Sjogren's syndrome Mixed connective tissue disease / overlap syndromes Undifferentiated connective tissue disease Idiopathic inflammatory myopathies
Drug-/chemical-related	Amphetamines Beta-blockers Bleomycin Cisplatin Clonidine Cyclosporine Interferons Methysergide Polyvinyl chloride
Conditions associated with increased plasma viscosity and reduced digital perfusion	Cryoglobulinaemia Cryofibrinogenaemia Paraproteinaemia Malignancy (including as a paraneoplastic phenomenon)
Other causes and associations	Carpal tunnel syndrome Frostbite Hypothyroidism

R. Gualtierotti et al. / *Microvascular Research* 113 (2017) 22–28

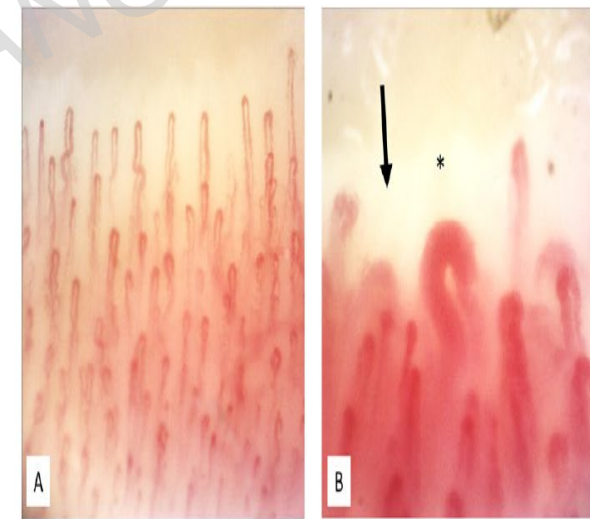
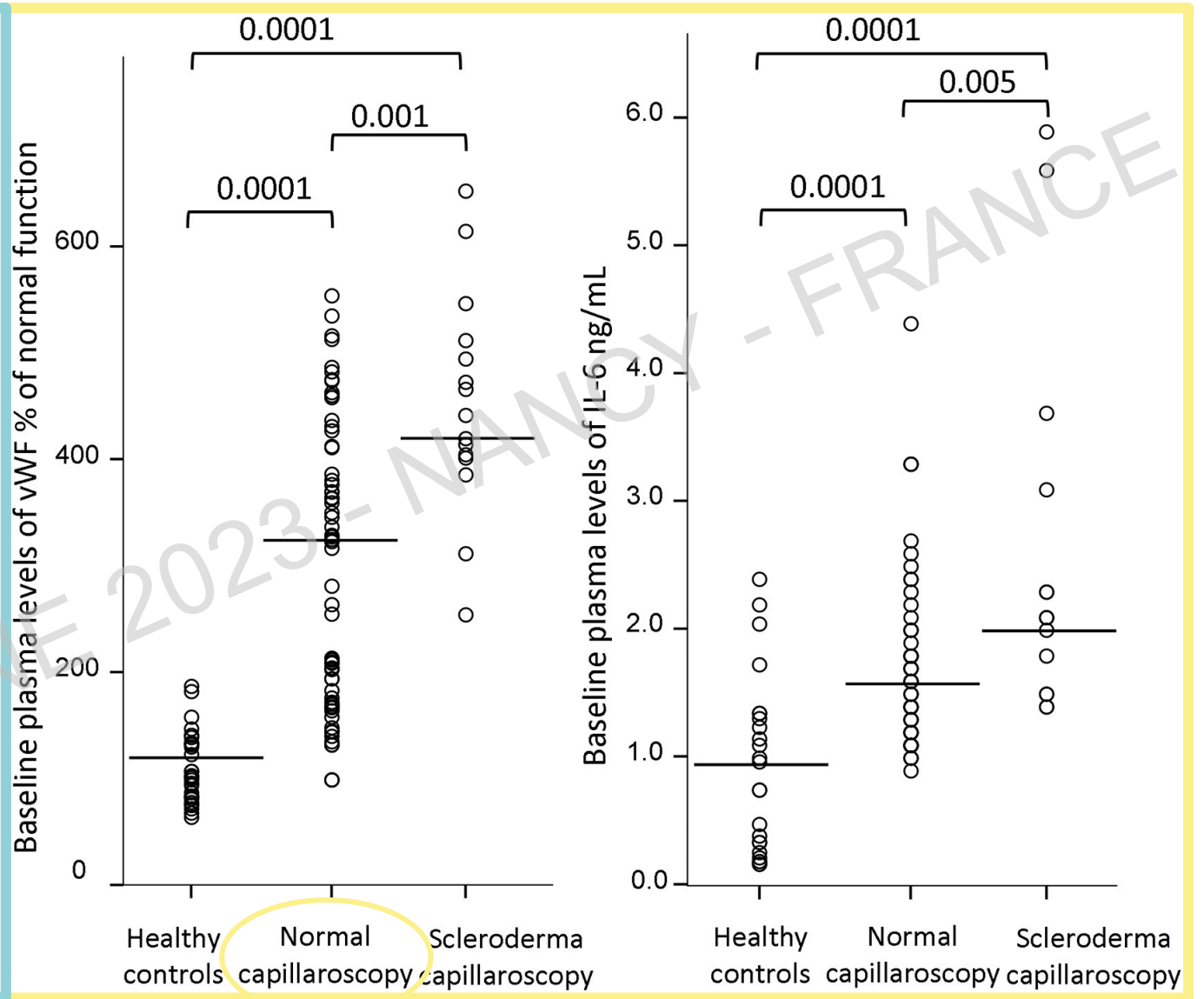
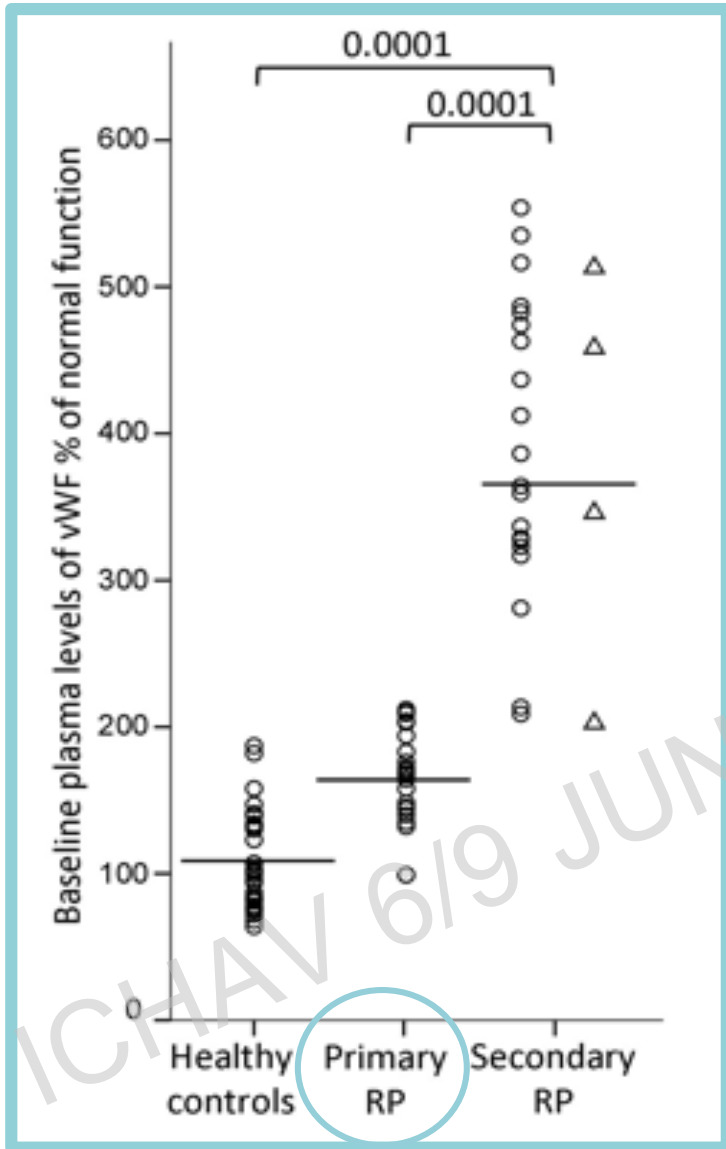


Fig. 1. Normal and scleroderma pattern at nailfold capillaroscopy. Panel A shows a capillaroscopic normal pattern, characterised by hairpin-shaped capillaries with regular morphology, dimensions and number; panel B shows an example of scleroderma pattern, characterised by avascular areas (arrow) and megacapillaries (asterisk); magnification 200×.

Gualtierotti, R., et al., *Detection of early endothelial damage in patients with Raynaud's phenomenon*. *Microvascular Research*, 2017. **113**: p. 22–28.



Gualtierotti, R., et al., *Detection of early endothelial damage in patients with Raynaud's phenomenon*. *Microvascular Research*, 2017. **113**: p. 22-28.

GRADING

Stockholm Workshop Scale 1987

Vascular component

SWS V0 no symptoms

SWS V1 occasionally episodes of finger blanching, only distal phalanges

SWS V2 occasionally episodes of finger blanching, distal and middle phalanges

SWS V3 frequent episodes of finger blanching involving all phalanges on most fingers

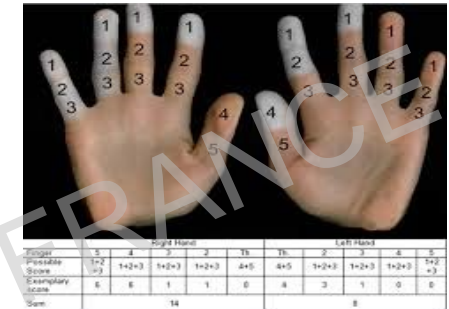
Sensorineural Component

0 SN Vibration exposed but no symptoms

1 SN Intermittent numbness with or without tingling

2 SN Intermittent or persistent numbness, reduced sensory perception

3 SN Intermittent or persistent numbness, reduced tactile discrimination and/or manipulative dexterity



International Consensus Criteria 2019

HAVS Vascular Component

ICC Stage	Description
0V	No attacks of blanching
1V	Digit blanching score 1-4
2V	Digit blanching score 5-12
3V	Digit blanching score >12

HAVS Neurological Component

ICC Stage	Description
0N	No numbness or tingling of digits
1N	Intermittent numbness and /or tingling of digits
2N	As in stage 1 but with sensory perception loss in at least one digit as evidenced by two or more validated methods such as monofilaments, thermal aesthesiometry and vibrotactile thresholds
3N	As in stage 2 but with symptoms of impaired dexterity and objective evidence of impaired dexterity by the Purdue pegboard test

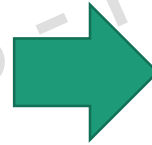
Anamnesis
Psychophysical tests

PROGNOSIS

Stop exposure...

..correct diagnosis?
..correct grading?

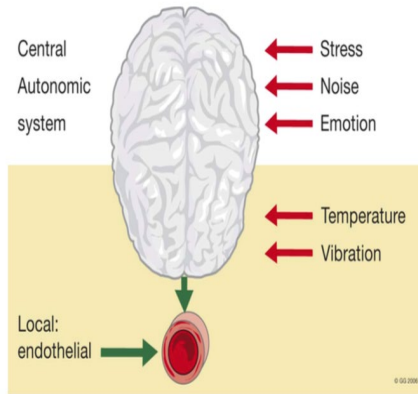
.....individual susceptibility?



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Vascular vs Sensorineural component



Vasoconstriction ← Vasodilation

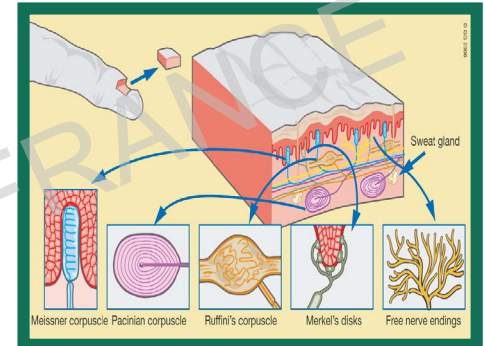
Nerve injury

Smooth muscle cell

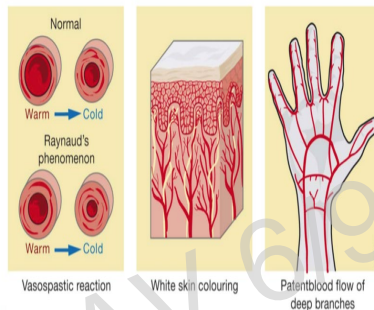
Endothelial cell

Stress/Injury

Inflammatory markers?
Growth mediating factors/repair?



	Aα Group I	AB II	AC III	C IV
Diameter (μm)	13-20	6-12	1-5	0.2-0.5
Speed (m/sec)	80-120	35-75	5-30	0.5-2
Sensory receptors	Proprioceptors	Mechanoreceptors	Pain, temperature	Temperature pain, itch



Raynaud's Phenomenon

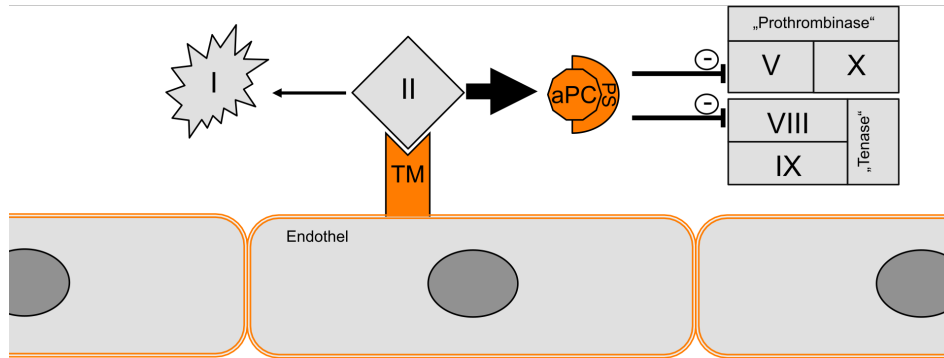
Endothelial function

Numbness/tingling

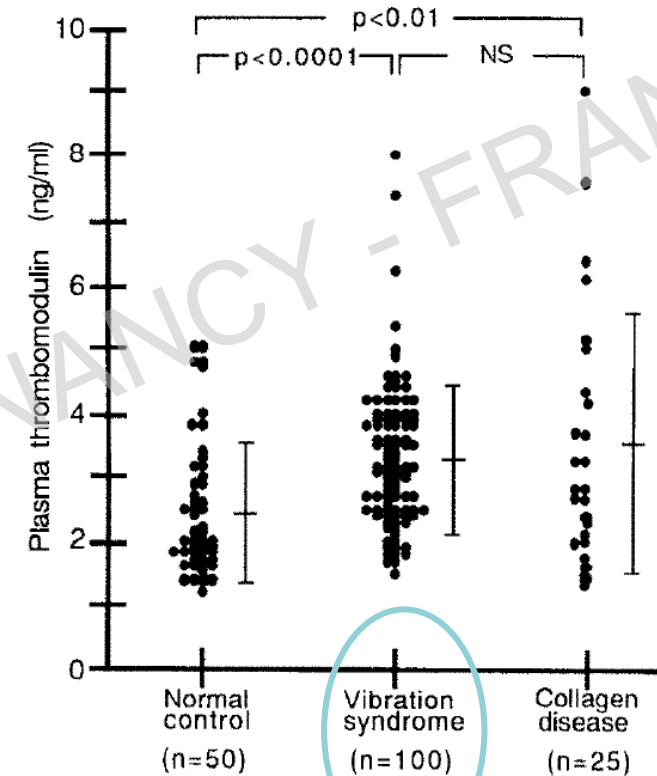
Increased cold sensitivity/cold intolerance?



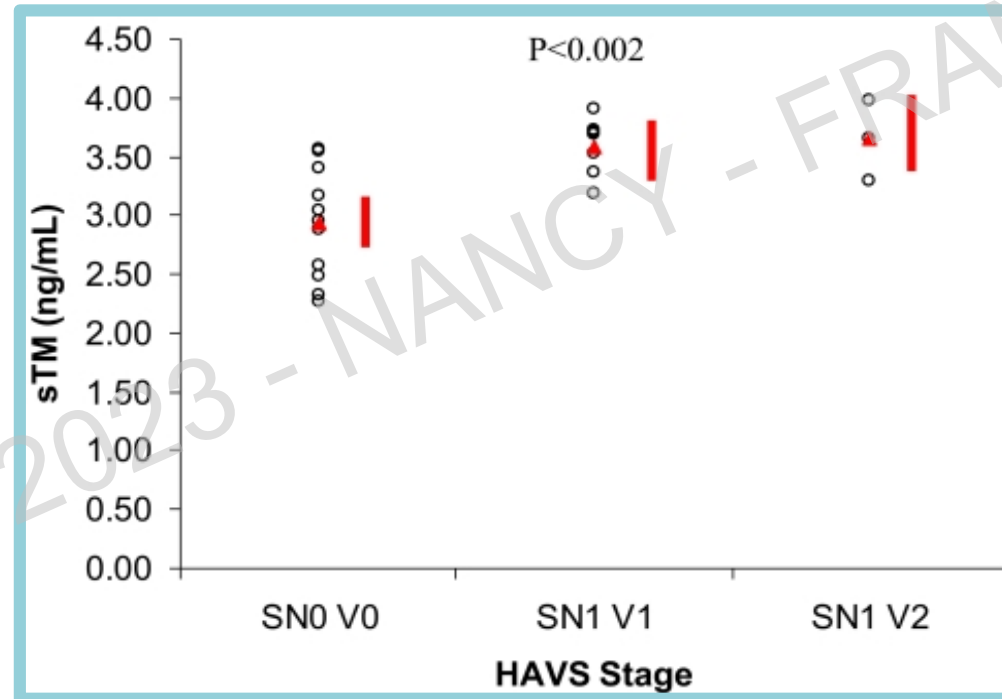
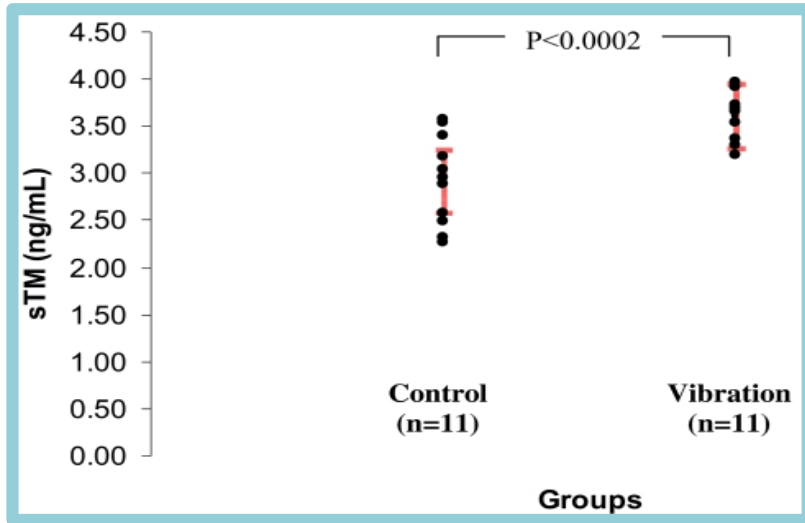
Thrombomoduline (TM)



Increased levels of soluble TM
– a marker for endothelial damage



Kanazuka, M., et al., *Increase in plasma thrombomodulin level in patients with vibration syndrome.* Thromb Res, 1996. 82(1): p. 51-6.



Kao, D.S., et al., *Serological tests for diagnosis and staging of hand-arm vibration syndrome (HAVS)*. Hand (N Y), 2008. **3**(2): p. 129-34.

Glial fibrillary acidic protein (GFAP)

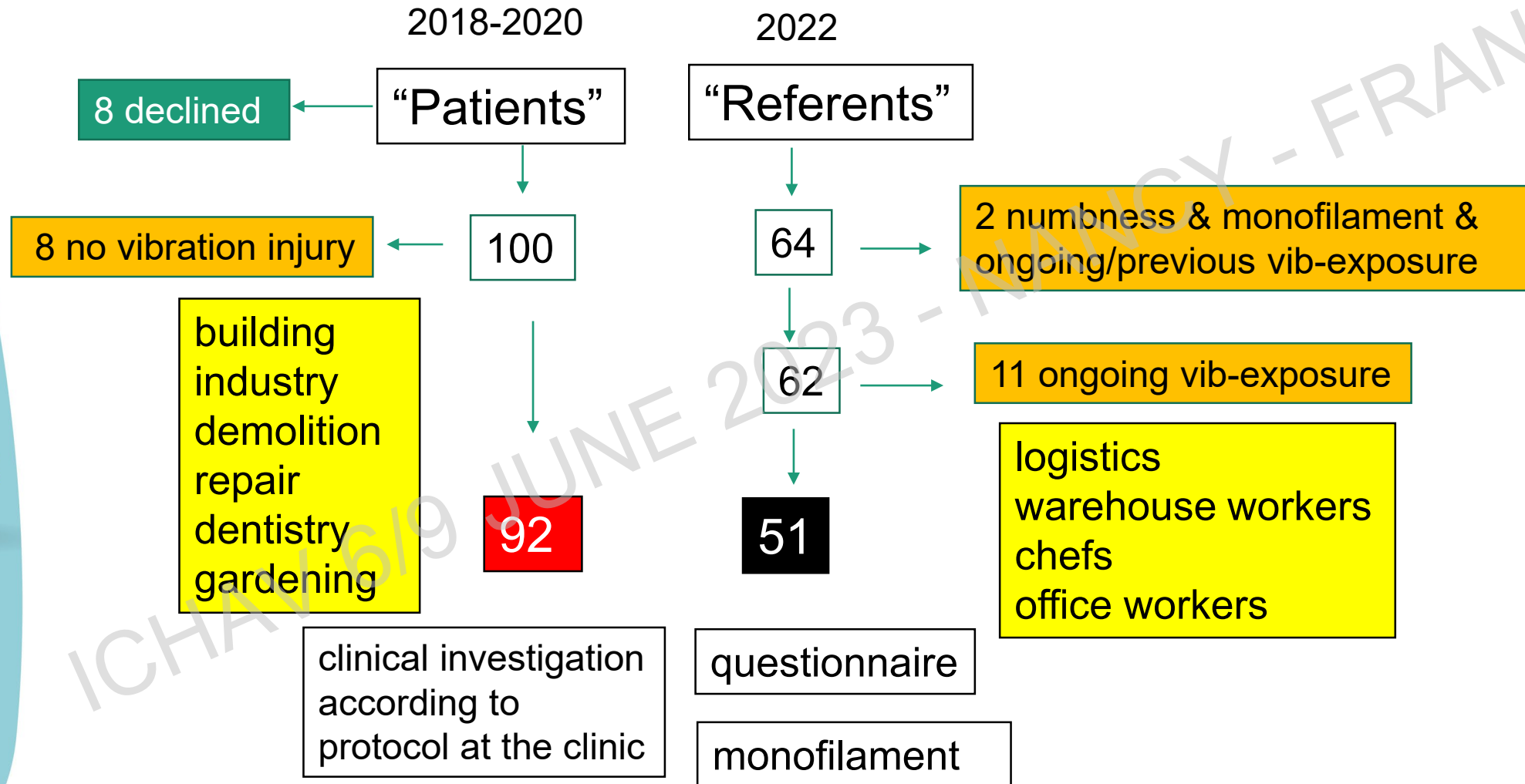
- a proposed marker for axonal damage
- detected in nerve biopsies in type 2 diabetes subjects and controls
- elevated serum levels correlate to decreased nerve action potentials

Rossor, A.M. and M.M. Reilly, Blood biomarkers of peripheral neuropathy. *Acta Neurologica Scandinavica*, 2022. 146(4): p. 325-331.

Ising, E., et al., Quantitative proteomic analysis of human peripheral nerves from subjects with type 2 diabetes. *Diabet Med*, 2021. 38(11): p. e14658.

Notturno, F., et al., Glial fibrillary acidic protein as a marker of axonal damage in chronic neuropathies. *Muscle Nerve*, 2009. 40(1): p. 50-4.

Study group



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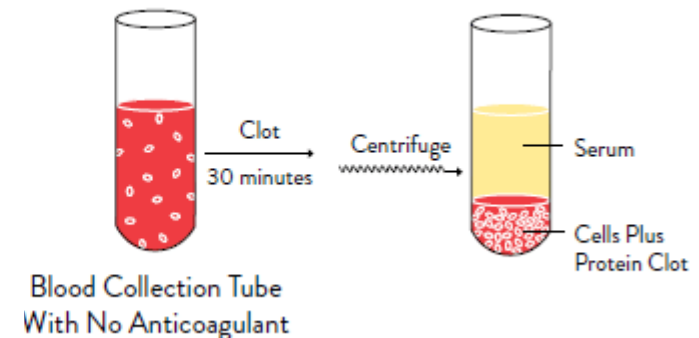
Biomarkers

Blood samples collected in the morning in 7 mL serum separation tubes with gel and clot activator

After 30 minutes serum was removed by centrifugation and the samples were stored at -80°C until analysis

ELISA kits: TM, GFAP

Values below the limit of detection (LOD) were awarded a value equal to half LODs (TM: 0.625 ng/ml, GFAP:31 pg/ml)



	Patients			Referents
	All n= 92	+RP n=45	-RP n=47	n=51
Age [years; median (range)]	45(21-64)	45 (24-64)	45 (21-64)	42 (26-62)
Females [n (%)]	6 (7)	1 (2)	5 (11)	9 (18)
Ongoing cigarette smoking [n (%)]	14 (15)	8 (18)	6 (13)	2 (4)
Other medical conditions				
Previous frostbites [n (%)]	10 ⁷ (11)	6 ⁴ (13)	4 ³ (9)	3 ¹ (6)
Cardiovascular disease [n (%)]	18 (20)	10 (22)	8 (17)	7(14)
Diabetes [n (%)]	6 (7)	4 (9)	2 (4)	2 (4)
Thyroid diseases [n (%)]	5 (5)	4 (9)	1 (2)	1 (2)
Rheumatic disease [n (%)]	0 (0)	0 (0)	0 (0)	0 (0)
Polyneuropathy [n (%)]	4 (4)	4 (9)	0	Missing
Symptoms				
Raynaud's phenomenon [n (%)]	45 (49)	100	0 (0)	5 (10)
Numbness/tingling [n (%)]	90 (98)	45 (100)	45 (96)	7 (14)
Nocturnal numbness/tingling	67 (73)	37 (82)	30 (64)	3 (6)
Cold intolerance [n (%)]	80 (87)	44 (98)	36 (77)	6 (12)
Impaired dexterity [n (%)]	65 (71)	36 (80)	29 (62)	4 (8)
Impaired grip strength [n (%)]	72 (78)	36 (80)	36 (77)	4 (8)
Clinical finding left or right hand				
Impaired perception of touch [n (%)]	45 (49)	29 (64)	16 (34)	6 (12)



	Patients	Referents	
Biomarker primary function	n=92	n=51	
	median (min-max)	Median (min-max)	p-value
<i>Endothelial dysfunction</i>			
TM (ng/mL)	5.5 (2.3–39)	4.3(0.3–34)	0.02
<i>Nerve injury</i>			
GFAP (pg/mL)	15(15–3100)	15(15–2800)	0.51

Mann-Whitney U test for comparison of distributions between groups

TM remained statistically significant after sensitivity analyses excluding (one at a time)

- Current smokers
- Females
- Subjects with concurrent diseases
- Previous frostbites

	HAVS patients with Raynauds Phenomenon n=45 ^a	HAVS patients without Raynauds Phenomenon n=47 ^b	Referents n=51 ^c	p-value			
	median (min-max)	median (min-max)	median (min-max)	p ^{abc}	p ^{ab}	p ^{ac}	p ^{bc}
Endothelial dysfunction							
TM (ng/mL)	6.1 (2.7–30)	5.2 (2.3–39)	4.3 (0.3–34)	0.004	0.02	<0.001	
Nerve injury							
GFAP (pg/mL)	15 (15–3100)	15 (15–2500)	15 (15–2800)	0.45			

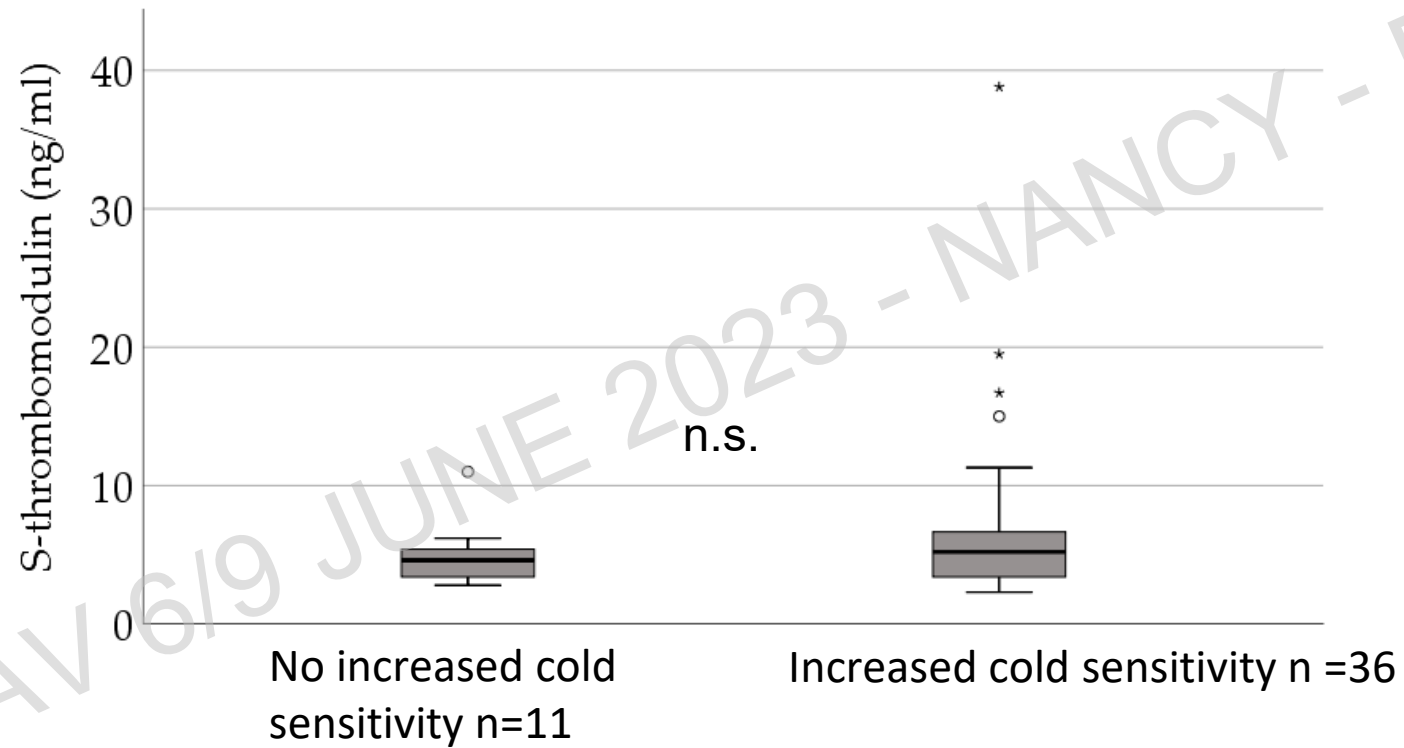
Kruskal Wallis for comparing distributions between groups

P-values in boldface denotes statistically significant differences

Post hoc analyses with Mann-Withney U test

TM remained significant after sensitivity analyses excluding current smokers, females and “concurrent diseases”, one at a time but not when excluding “previous frostbites” (p=0.06)

Patients without Raynaud Phenomenon



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Clinical implications of biomarkers

- Used as an objective method for diagnosis and grading?
- Further explain individual prognosis and susceptibility?
- Identifying early injury? – Preventive work
- In the future: development of pharmacological treatments??





Thank you!

Elizabeth Huynh for analyses of biomarkers

Ulla Andersson, Else Åkerberg Krook,

Eva Assarsson, Anna Larsson for collection of blood samples and handling of data

The patients and referents participating in the study

AFA insurance

