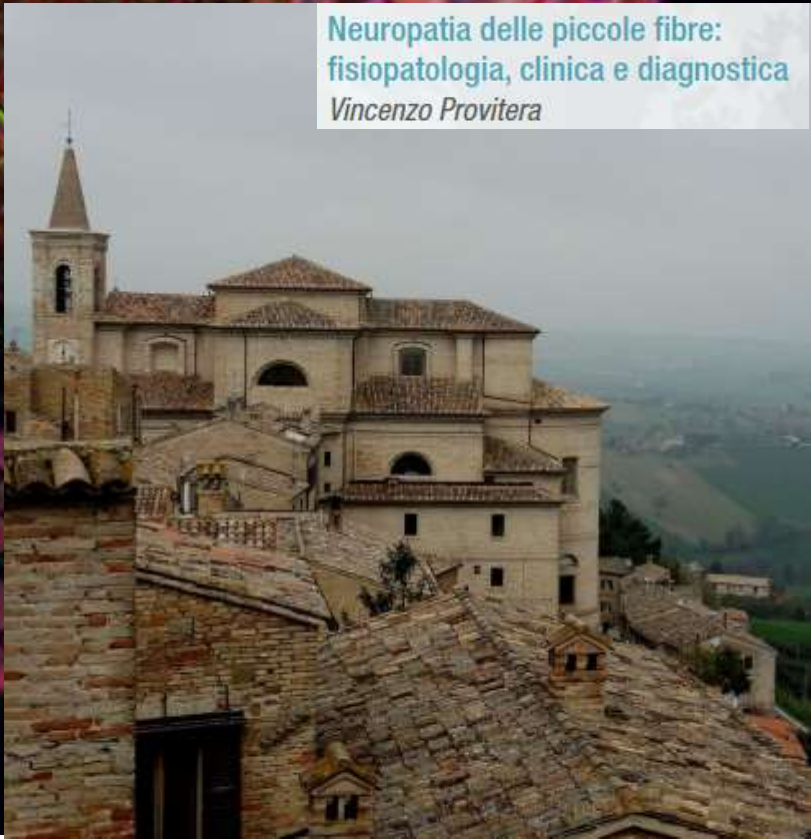
Corso AINV.
La disautonomia nella pratica clinica: diagnosi e strategie terapeutiche

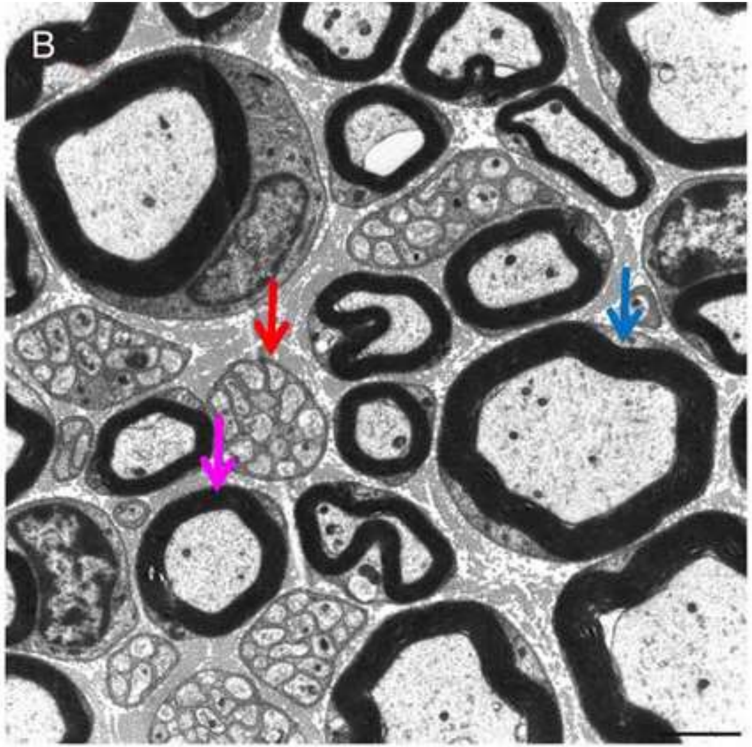


Neuropatia delle piccole fibre: fisiopatologia, clinica e diagnostica

Vincenzo Provitera

Neuropatia delle piccole fibre

- Coinvolgimento selettivo o prevalente delle fibre mieliniche di piccolo calibro e amieliniche.

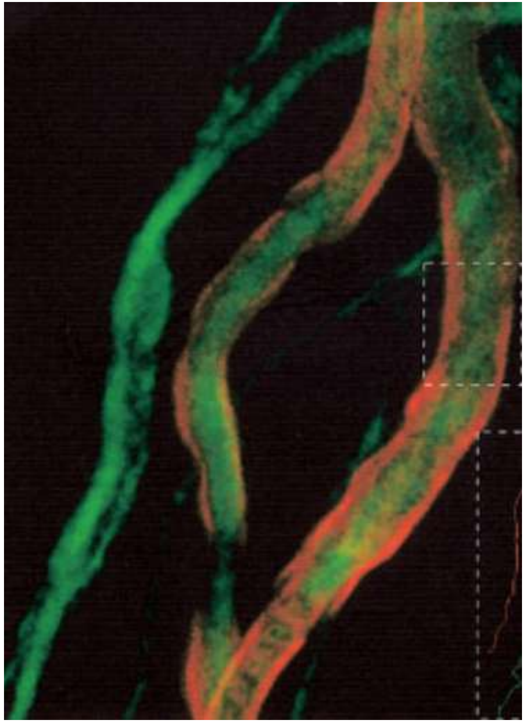


FIBRE SENSITIVE

STIMOLI TERMICI	**Caldo**	→	C
	Freddo	→	Aδ
	Dolore da Caldo	→	C
	Dolore da freddo	→	Aδ
STIMOLI MECCANICI	*Tattili*	→	Aβ
	Vibratori	→	Aβ
	Dolore meccanico	→	Aδ

FIBRE AUTONOMICHE

VISCEROEFFETRICI SECRETOMOTORIE	**Noradrenergiche**	→	C
	Colinergiche	→	C



La dimensione del problema

Netherlands

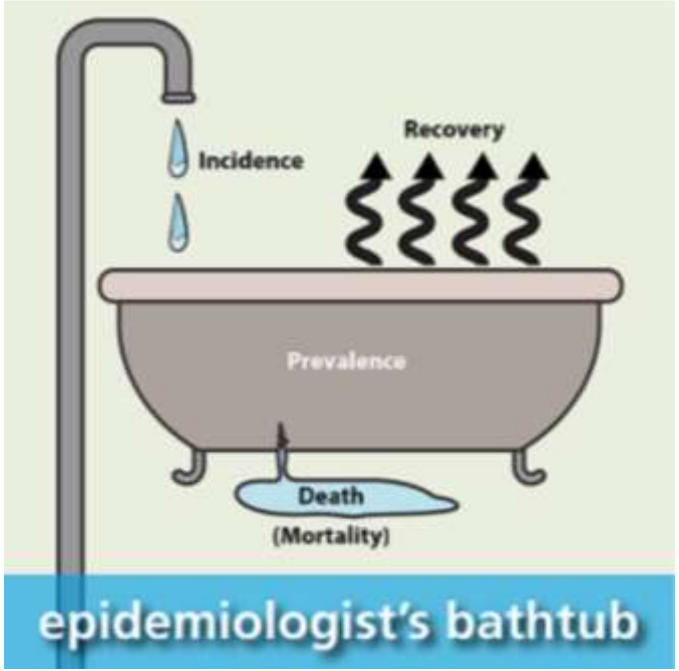
Neurology 2013 Peters MJ et al.

INCIDENZA

11.7 casi/100,000 abitanti/anno

PREVALENZA

52.9 casi/100.000


Incidence
Recovery
Prevalence
Death
(Mortality)
epidemiologist's bathtub

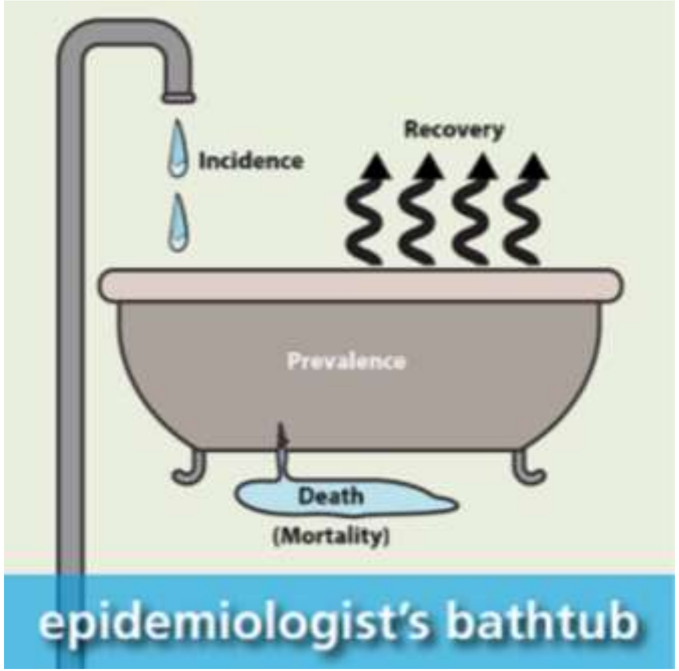
La dimensione del problema

INCIDENZA

7000 nuovi casi / anno

PREVALENZA

> 30000


Incidence
Recovery
Prevalence
Death
(Mortality)
epidemiologist's bathtub

Eziopatogenesi

Metabolic
- Impaired glucose tolerance
- Diabetes mellitus
- Rapid glycaemic control
- Vitamin B12 deficiency
- Dyslipidaemia
- Hypothyroidism
- Chronic kidney disease

Infections
- HIV
- Hepatitis C
- Influenza

Toxins and drugs
- Anti-retrovirals
- Antibiotics—metronidazole, nitrofurantoin, linezolid
- Chemotherapy—bortezomib
- Flecainide
- Statin
- Alcohol
- Vitamin B6 toxicity

Immune mediated
- Coeliac disease
- Sarcoidosis
- Sjögren’s syndrome
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Vasculitis
- Inflammatory bowel disease
- Paraneoplastic
- Monoclonal gammopathy/amyloid

Hereditary/genetic
- Na_v1.7 mutations
- Na_v1.8 mutations
- Familial amyloid polyneuropathy
- Fabry’s disease
- Tangier’s disease

Idiopathic
- Idiopathic small fibre neuropathy
- Burning mouth syndrome

CAUSE
EFFECT

Themistocleous AC, et al.
Pract Neurol 2014;14:368–379

Caratteristiche cliniche

DISTURBI SENSITIVI

- **Dolore**: peggiora nelle ore notturne
- Intolleranza al contatto con indumenti o lenzuola
- Sindrome delle gambe senza riposo
- Sensazione di intorpidimento, di “fascia” o di “freddo”

✓ **Dolore urente**

✓ Freddo doloroso

✓ Prurito

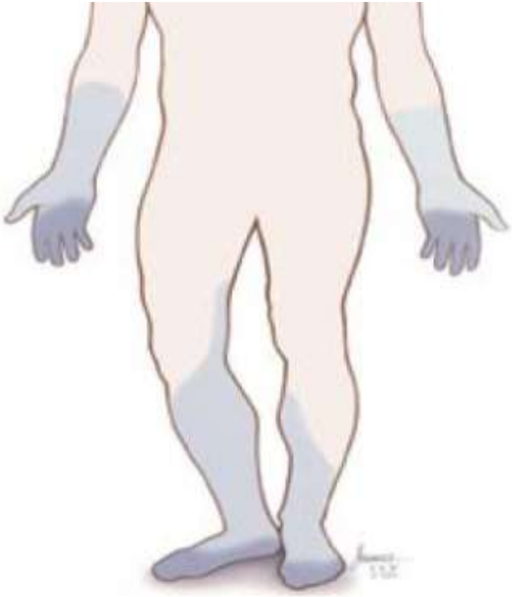
✓ Stretta dolorosa

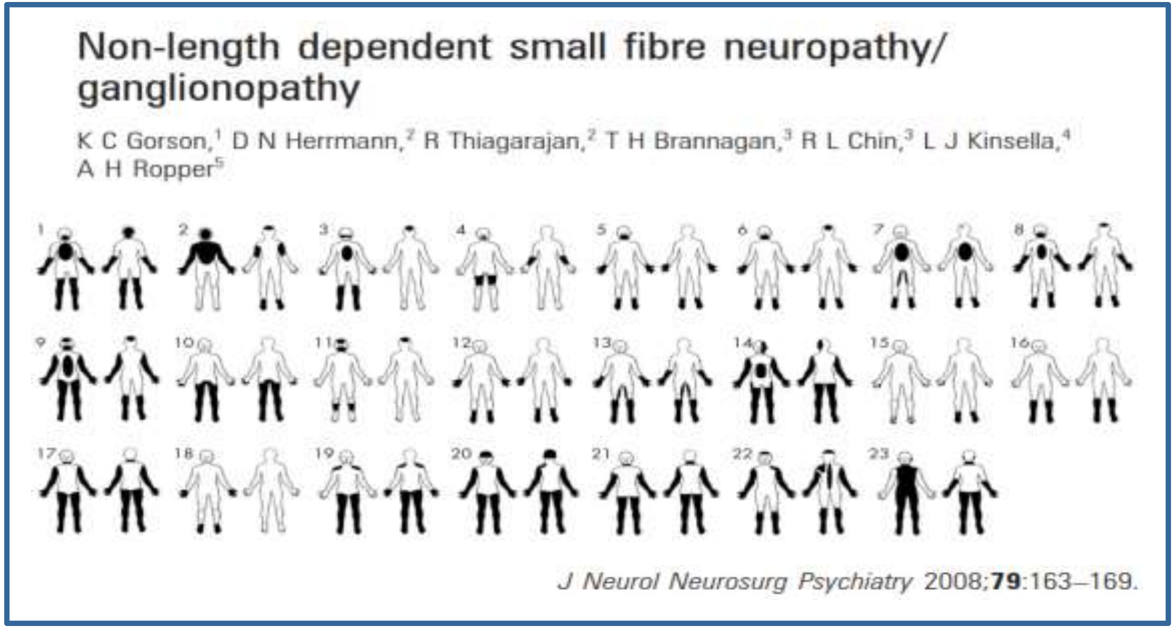
✓ Dolore lancinante

le neuropatie delle piccole fibre (SFN)

sintomi e segni_distribuzione

length-dependent
distribution





Non-length dependent small fibre neuropathy/ ganglionopathy

K C Gorson,[1] D N Herrmann,[2] R Thiagarajan,[2] T H Brannagan,[3] R L Chin,[3] L J Kinsella,[4]
A H Ropper[5]

1
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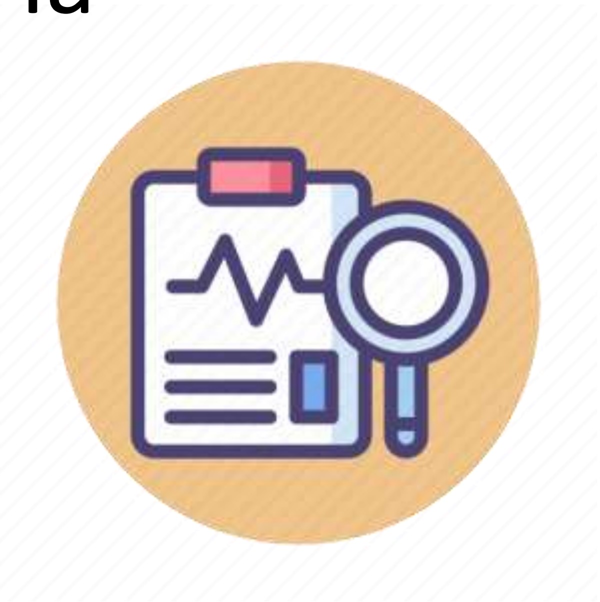
J Neurol Neurosurg Psychiatry 2008;**79**:163–169.

Small fiber neuropathy
Diagnostic criteria

Almeno due criteri tra:

1) ipoestesia termica/dolorifica e/o iperalgesia e/o allodinia;
2) Anomalie al *quantitative sensory testing* al sito distale
3) Ridotta densità di IENF alla gamba

Assenza di segni di coinvolgimento di fibre di grosso calibro (atassia, areflessia, apallestesia…). Normale neurografia.



Besta criteria. Devigili et al., 2008

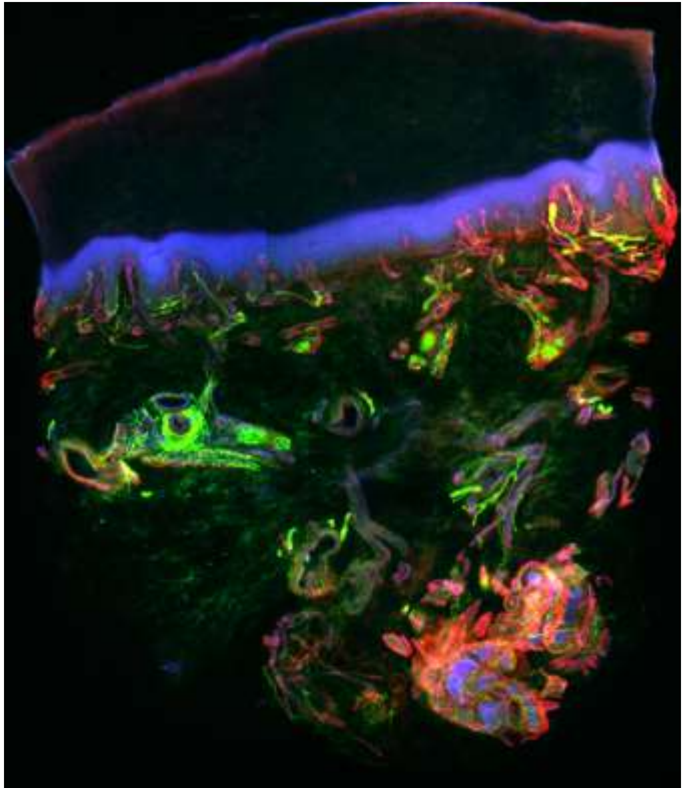
Small fiber neuropathy Diagnostic criteria

POSSIBILE	Sintomi o segni di coinvolgimento delle piccole fibre o entrambi
PROBABILE	Segni di coinvolgimento delle piccole fibre e normali velocità di conduzione
DEFINITO	Criteri di probabilità + Anomalie del QST o Riduzione delle fibre epidermiche alla gamba

NEURODIAB (Tesfaye et al., 2010)

Why skin biopsy?

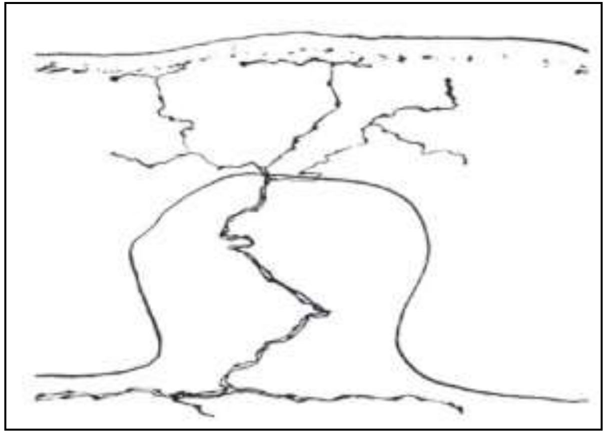
- ✓ minimally invasive
- ✓ more sensitive than sural nerve
- ✓ possibility to recognize fibers from their target



Epidermal nerve fibers

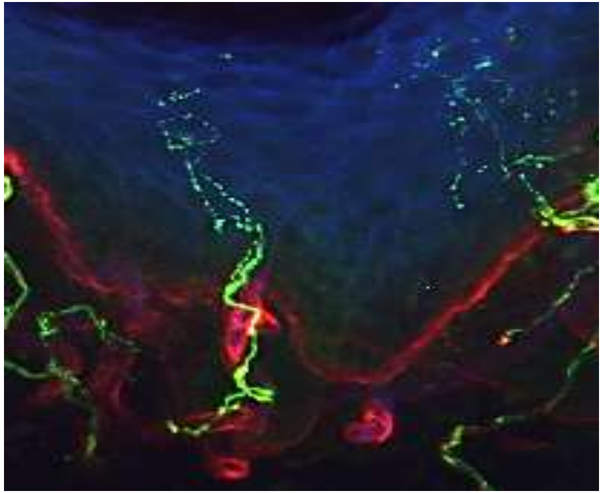
- ✓ Paul Langerhans 1868
- ✓ Arthur and Shelley 1959

“ *First observations of Epidermal Nerve Fiber* ” ►



- ✓ Wang et al. 1990

“ *Demonstration of Epidermal Nerve Fiber using PGP* ” ►

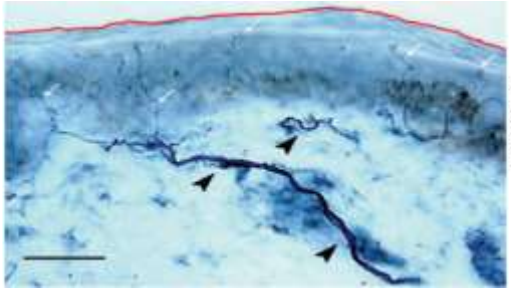


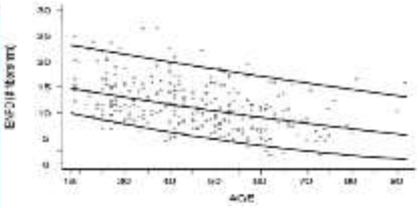
Method standarditation

- ✓ Kennedy and Crabb 1993
- ✓ Mc Carthy et al. 1995

Normative data

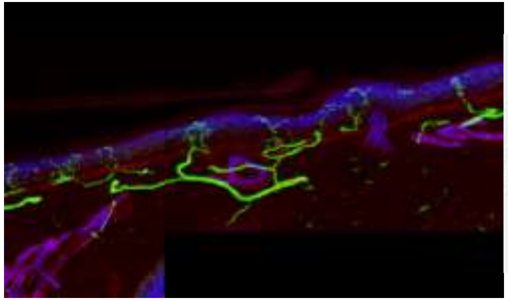
Bright-field

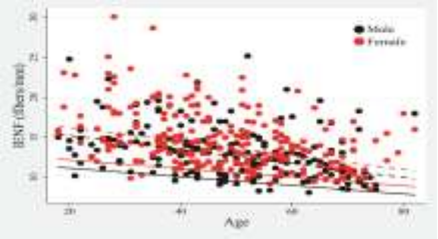




Lauria G et al. , J Peripher Nerv Syst. 2010

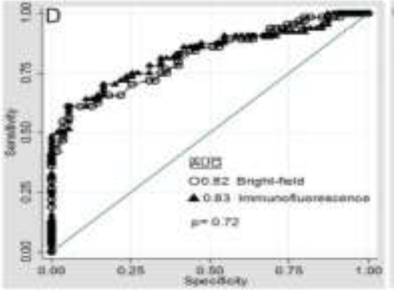
Immunofluorescence

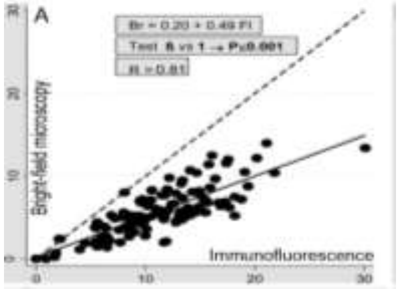




Provitera V et al. , Eur J Neurol. 2016

- ✓ *about 1 fiber/mm more in woman*
- ✓ *0.54 fiber/mm loss for decade*

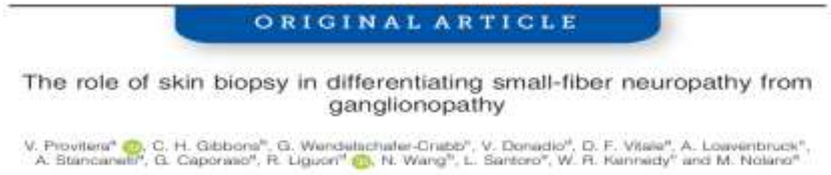




Bright-field VS Immunofluorescence

- ✓ Same diagnostic efficiency
- ✓ FL/BF ratio 2 : 1

Nolano M et al. , J Peripher Nerv Syst. 2015

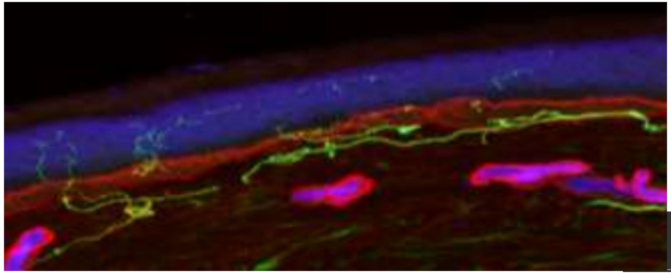


ORIGINAL ARTICLE

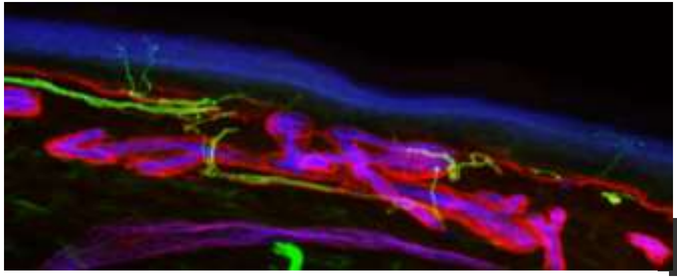
The role of skin biopsy in differentiating small-fiber neuropathy from ganglionopathy

V. Provitera, C. H. Gibbons, G. Wendelschafer-Crabb, V. Donadio, D. F. Vitale, A. Loavenbruck, A. Stancanelli, G. Caporaso, R. Liguori, N. Wang, L. Santoro, W. R. Kennedy and M. Nolano

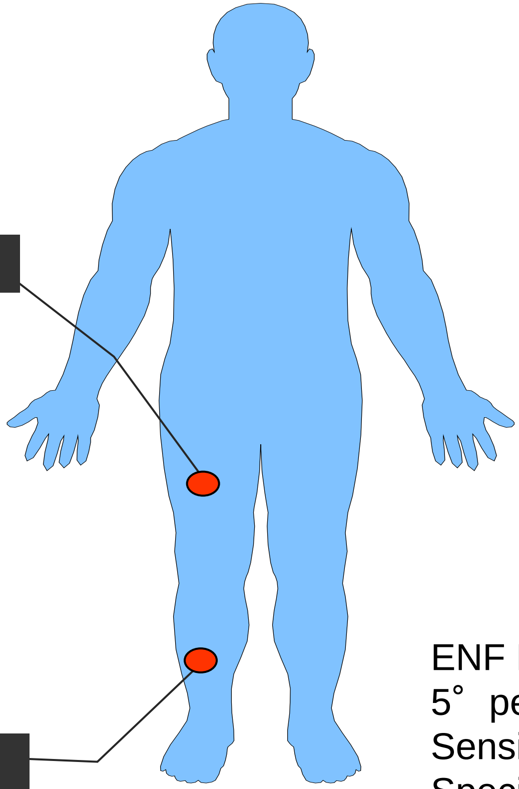
SFN

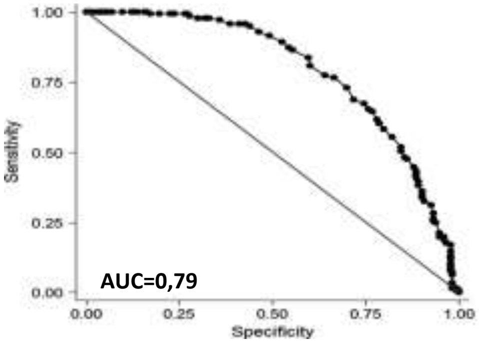


Thigh



Leg





AUC=0,79

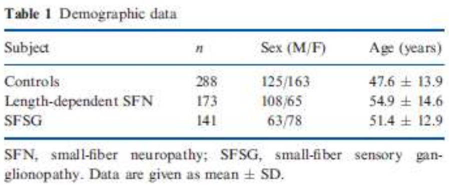


Table 1 Demographic data

Subject	*n*	Sex (M/F)	Age (years)
Controls	288	125/163	47.6 ± 13.9
Length-dependent SFN	173	108/65	54.9 ± 14.6
SFSG	141	63/78	51.4 ± 12.9

SFN, small-fiber neuropathy; SFSG, small-fiber sensory ganglionopathy. Data are given as mean ± SD.

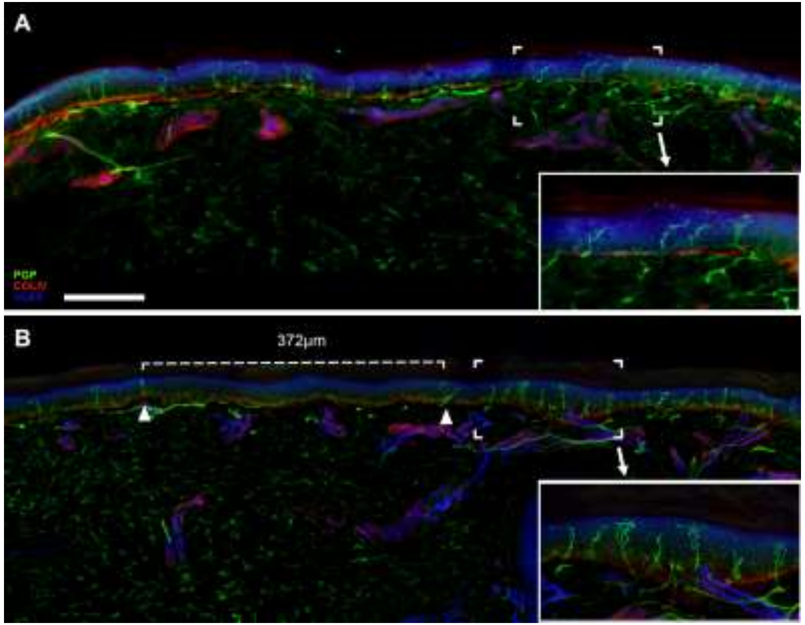
ENF Leg/thigh ratio = 0.67±14

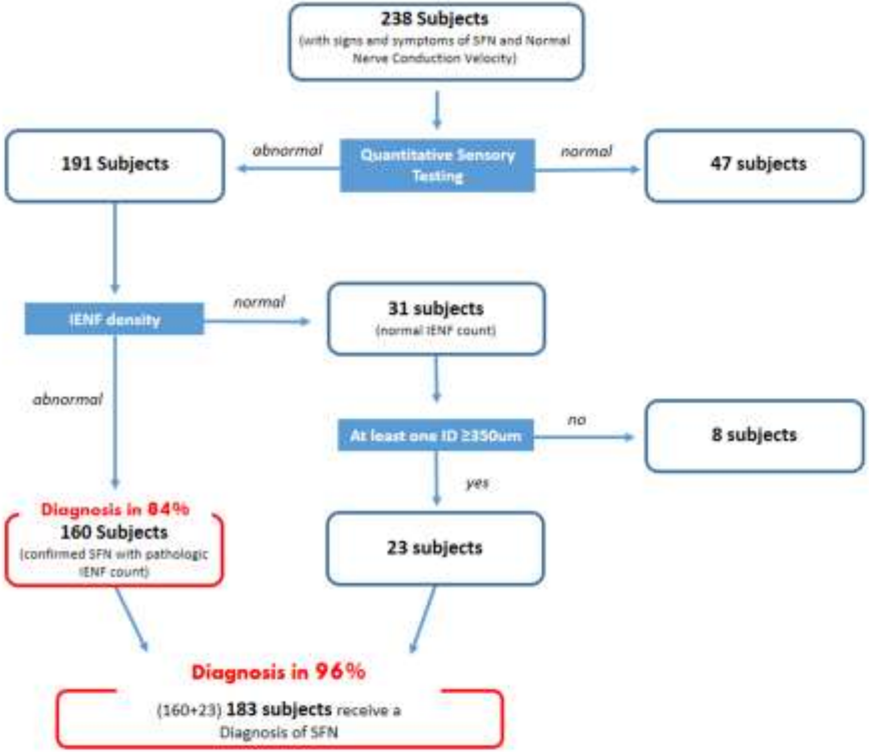
5° percentile cutoff = 0.48

Sensitivity: 0.80

Specificity: 0,61

Adjunctive criteria to increase skin biopsy diagnostic efficiency





238 Subjects
(with signs and symptoms of SFN and Normal Nerve Conduction Velocity)

Quantitative Sensory Testing

abnormal → **191 Subjects**

normal → **47 subjects**

IENF density

normal → **31 subjects** (normal IENF count)

At least one ID ≥350um

no → **8 subjects**

yes → **23 subjects**

abnormal → **Diagnosis in 84%**
160 Subjects
(confirmed SFN with pathologic IENF count)

Diagnosis in 96%

(160+23) **183 subjects** receive a Diagnosis of SFN

QUANTITATIVE SENSORY TESTING (QST)

- Soglie Tattili:

MONOFILAMENTI CALIBRATI DI SEMMES WEINSTEIN

- Pinprick:

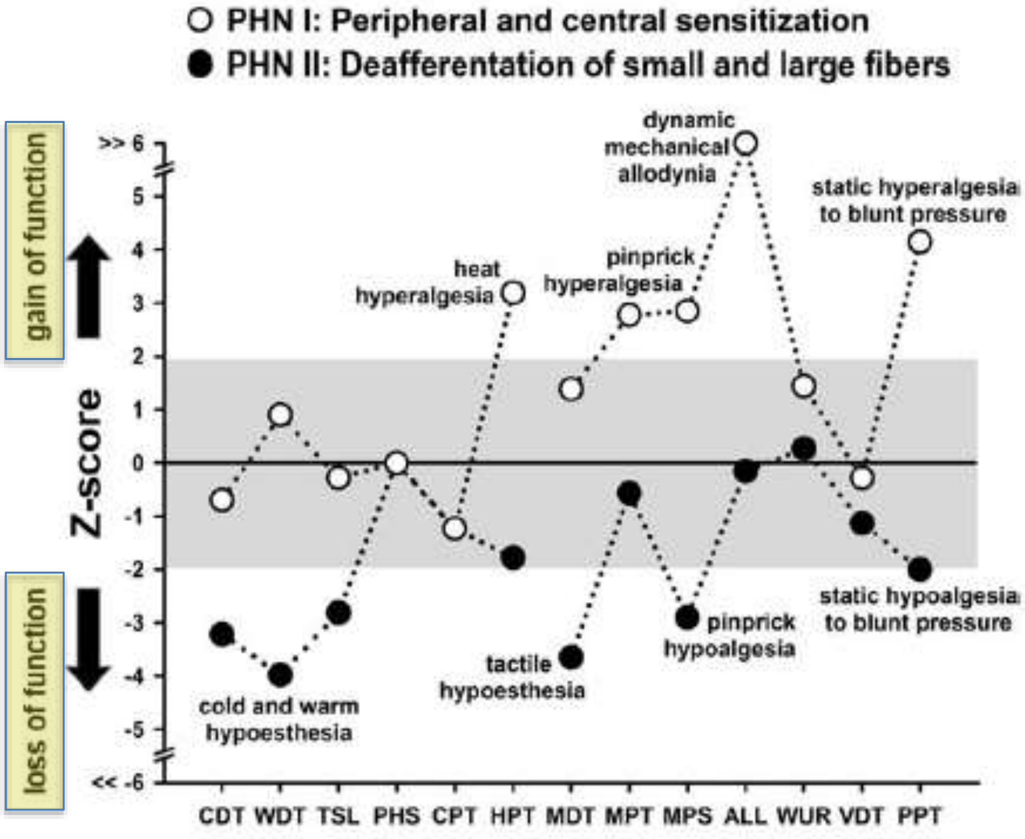
MONOFILAMENTO CALIBRATO CON PUNTA METALLICA DI 50 MICRON

- Soglie Termiche:

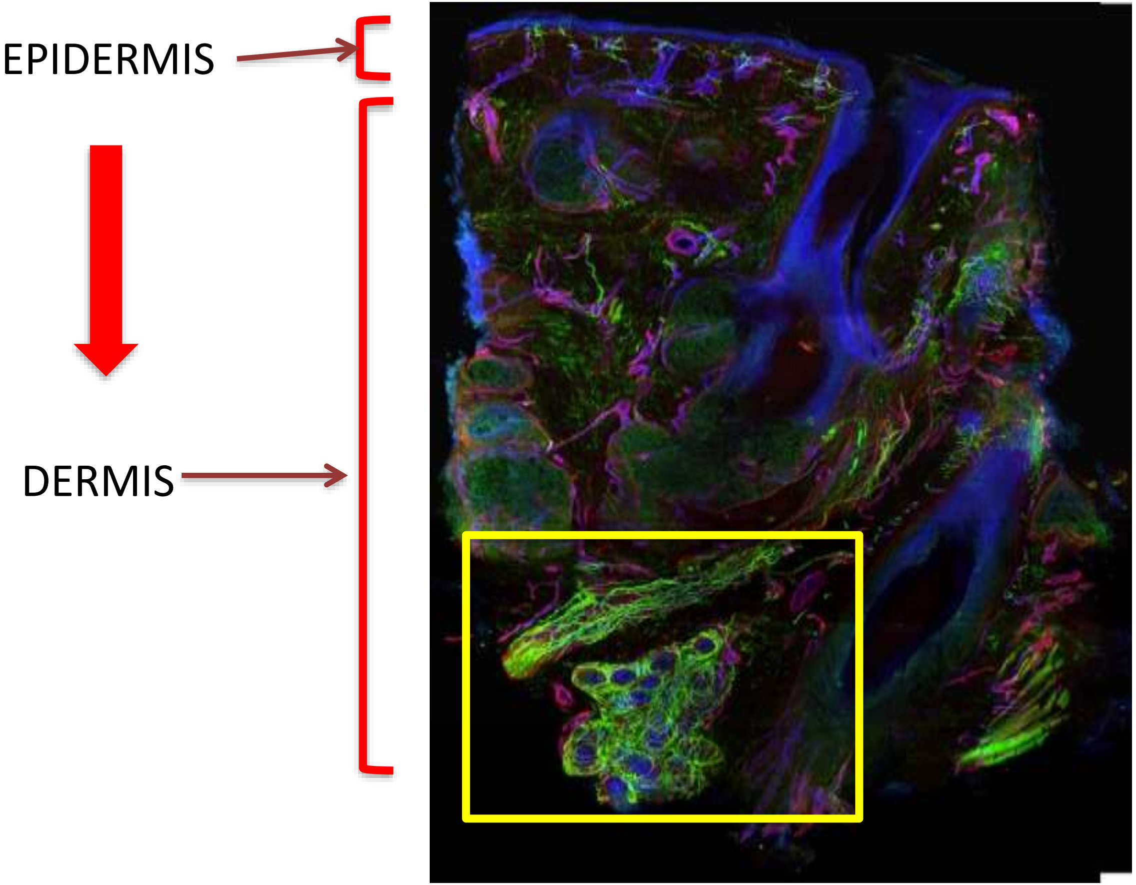
CASE IV - 4-2-1 STEPPING ALGORITHM
TSA 2001 - METODO DEI LIMITI – METODO DEI LIVELLI

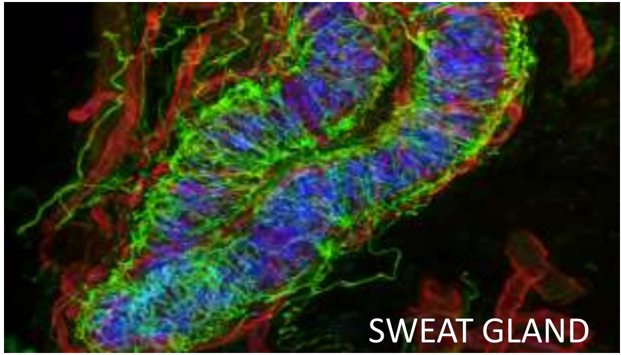
DFNS Sensory Profile

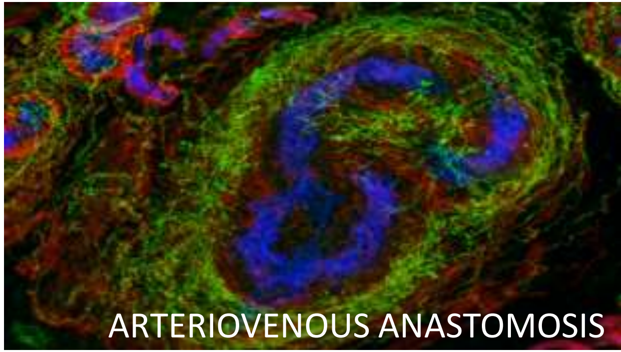
- Cold detection threshold (CDT)
- Warm detection threshold (WDT)
- Thermal sensory limen (TSL)
- Paradoxical heat sensations (PHS)
- Cold pain threshold (CPT)
- Heat pain threshold (HPT)
- Tactile detection thresholds (MDT)
- Mechanical pain threshold (MPT)
- Mechanical pain sensitivity (MPS)
- Dynamic mechanical allodynia (DMA)
- Wind-up ratio (WUR)
- Vibration detection threshold (VDT)
- Pressure pain threshold (PPT)

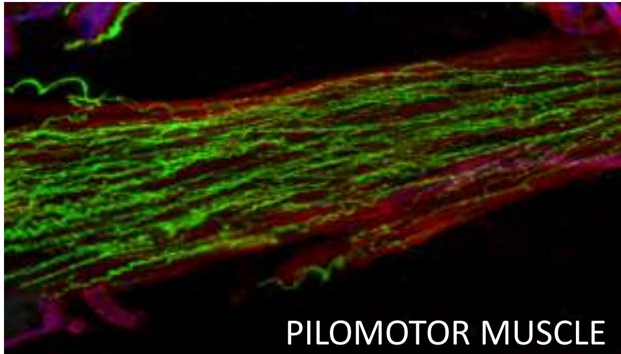


THE RICH SUPPLY OF AUTONOMIC NERVES IN THE DEEPER CUTANEOUS LAYERS


EPIDERMIS
DERMIS


SWEAT GLAND

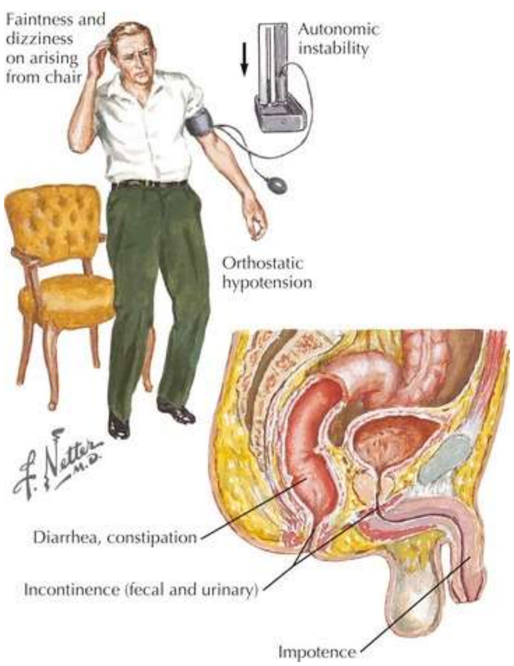

ARTERIOVENOUS ANASTOMOSIS


PILOMOTOR MUSCLE

Caratteristiche cliniche

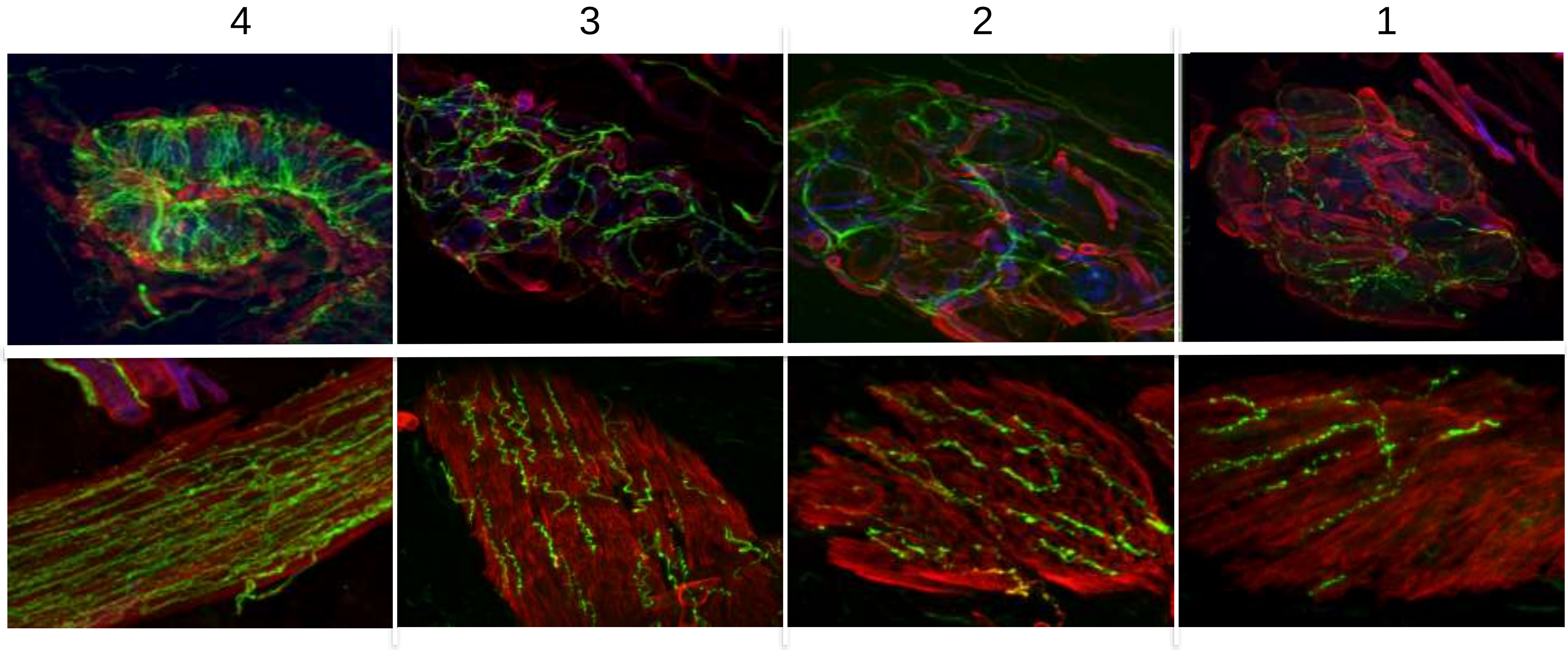
SINTOMI DI DISFUNZIONE AUTONOMICA:

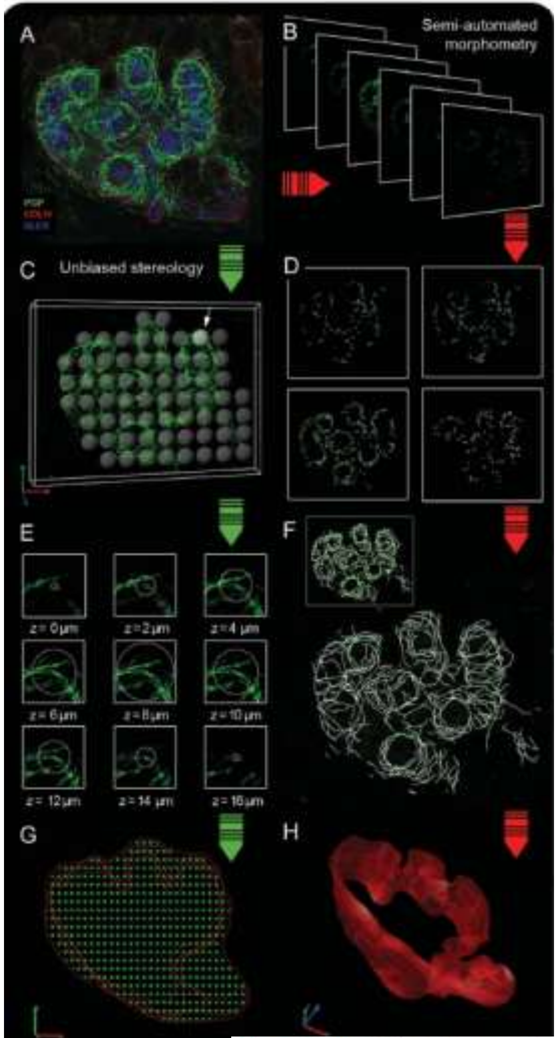
- Ipo o iperidrosi, diarrea o stipsi, gastroparesi
- Sintomi ortostatici
- Incontinenza o ritenzione urinaria
- Visione offuscata, arrossamenti facciali transitori
- Disfunzione sessuale, disturbi vasomotori acrali


Faintness and dizziness on arising from chair
Autonomic instability
Orthostatic hypotension
Diarrhea, constipation
Incontinence (fecal and urinary)
Impotence

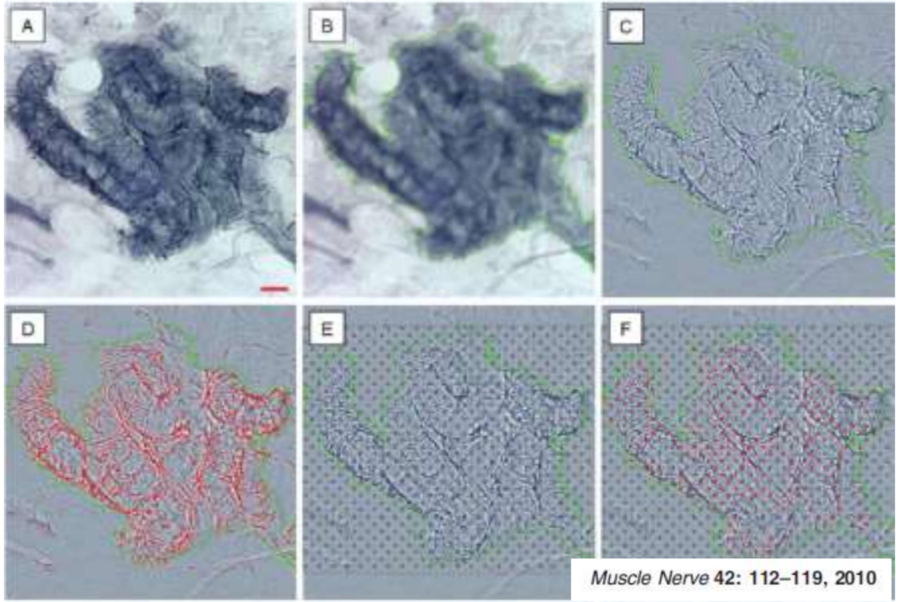
Autonomic innervation

Semiquantitative assessment

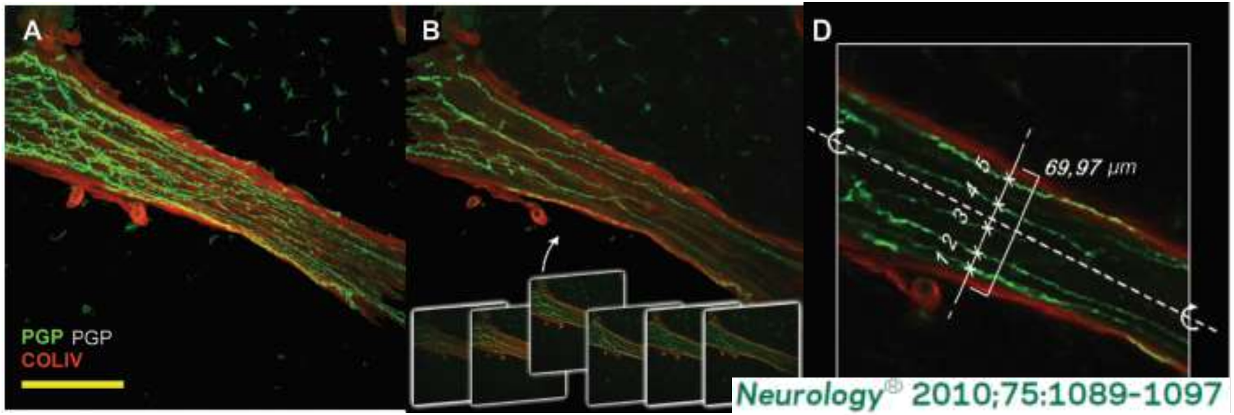



A
PGP
COLIV
B
Semi-automated morphometry
C
Unbiased stereology
D
E
z = 0µm
z = 2µm
z = 4 µm
z = 6µm
z = 8µm
z = 10 µm
z = 12µm
z = 14 µm
z = 16µm
F
G
H

Neurology® 2014;82:1-7

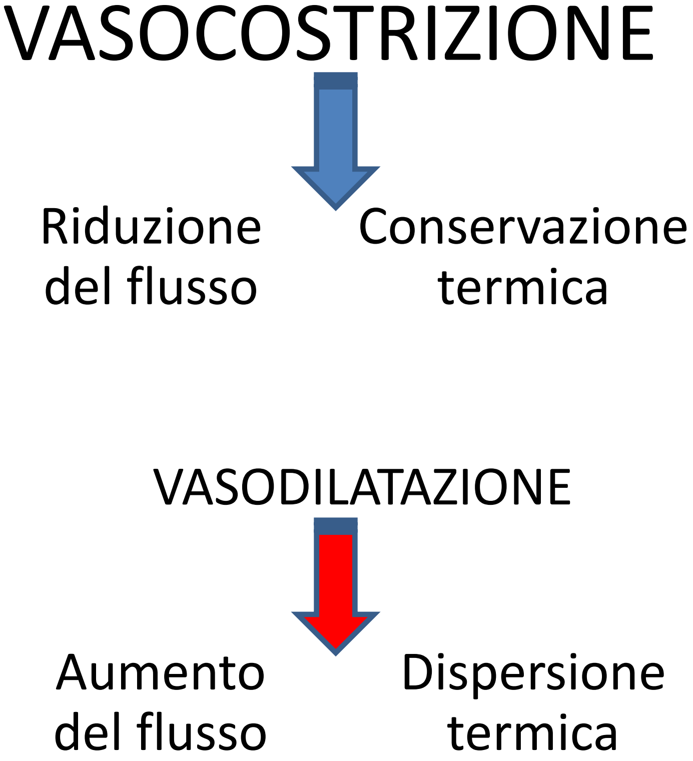


Muscle Nerve **42: 112–119, 2010**


A
B
D
69,97 µm
1
2
3
4
5
PGP PGP
COLIV

Neurology® 2010;75:1089-1097

Il controllo del flusso sanguigno nella cute



VASOCOSTRIZIONE

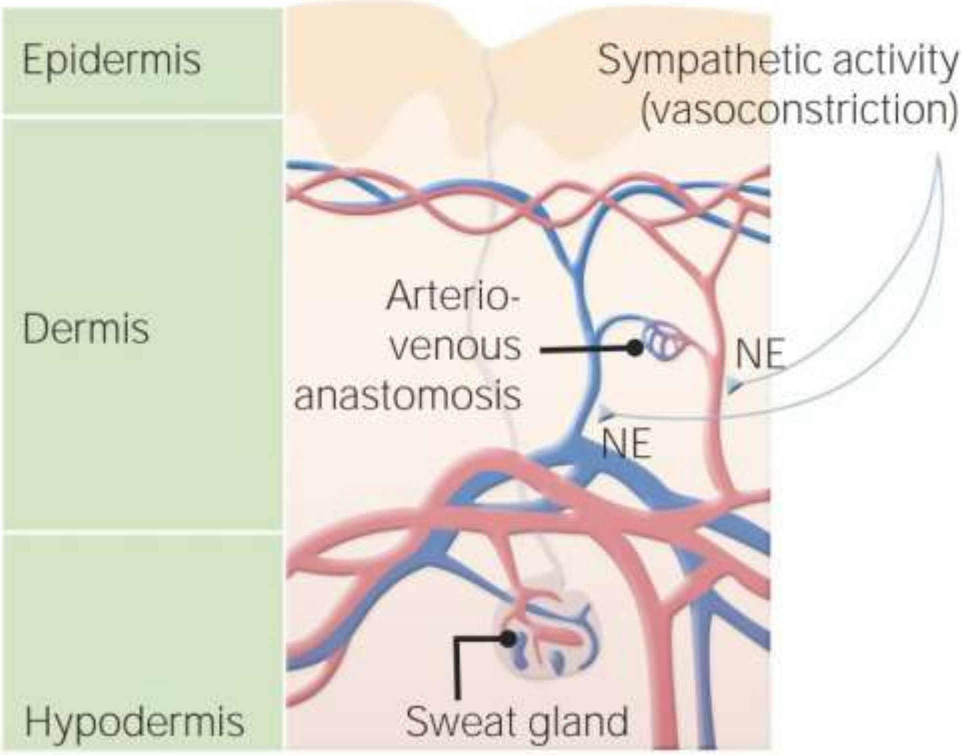
Riduzione del flusso

Conservazione termica

VASODILATAZIONE

Aumento del flusso

Dispersione termica


Epidermis
Dermis
Hypodermis
Sympathetic activity (vasoconstriction)
Arterio-venous anastomosis
NE
NE
Sweat gland

COLD
WARM
HOT

VASOCOSTRIZIONE

- Freddo
- Respiro profondo
- Stress emotivo
- Stimoli di arousal
- Cambi di posizioni degli arti

TRASMISSIONE
ADRENERGICA
alpha1 e alpha2

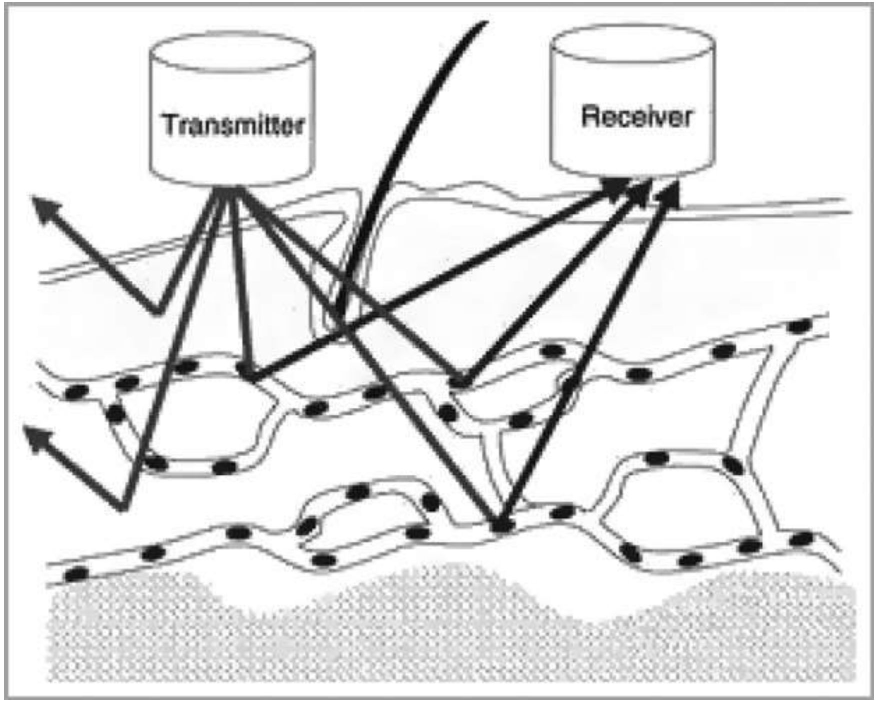
VASODILATAZIONE

- Aumento temp. corporea
- Riscaldamento locale
- Dolore

CO-TRASMISSIONE
COLINERGICA
Ach, NO, neuropeptidi

FLUSSIMETRIA LASER DOPPLER

- Trasmissione di raggio laser
- Registrazione della variazione in lunghezza d’onda rispetto al raggio incidente


Transmitter
Receiver

Variazione del flusso ↑ Maggiore wL shift

IL FLUSSIMETRO LASER DOPPLER

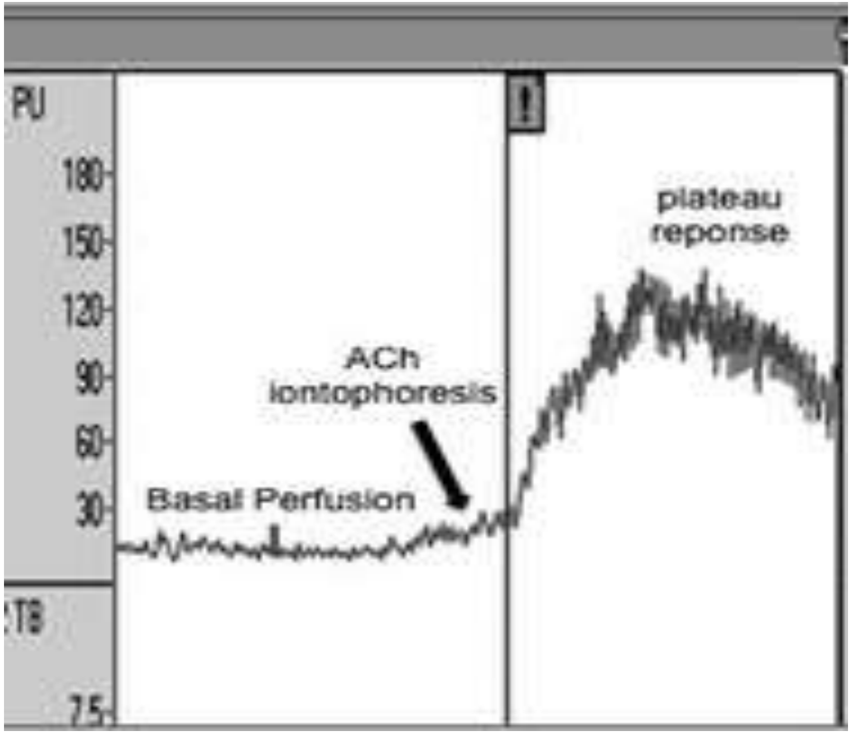
Moor Instruments
moorLAB
SERVER
F
POWER
Laser Doppler Perfusion Monitor

TSD140
TSD142
TSD143
TSD146

- UNITA’ CENTRALE
- SONDE A FIBRA OTTICA
- MODULI PER STIMOLAZIONE TERMICA IONOFORESI
- SOFTWARE PER REGISTRAZIONE E ANALISI DEL SEGNALE

IL SEGNALE LASER DOPPLER

- Campo d’azione 1-1,5 mm di profondità
- Registrazione della variazione di flusso in unità convenzionali di perfusione

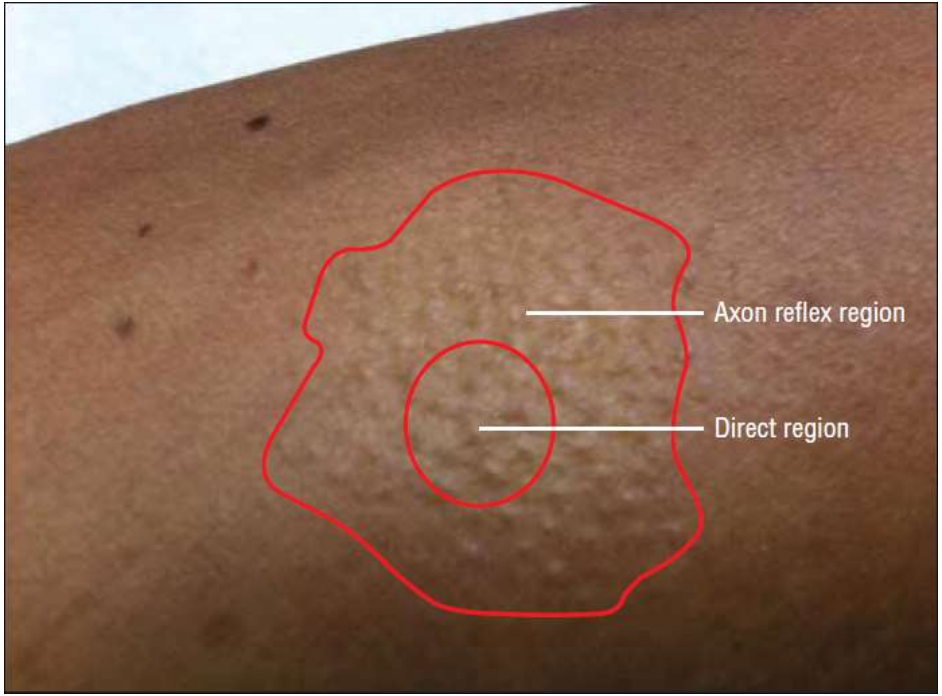


PRINCIPALI PROTOCOLLI

FUNZIONE	STIMOLO	RISULTATO
VASODILATAZIONE	STIMOLO TERMICO	INCREMENTO
VASODILATAZIONE	ACh Ionoforesi	INCREMENTO
VASOCOSTRIZIONE	AROUSAL/RESPIRO	RIDUZIONE
VASOCOSTRIZIONE	POSTURA 3-5’	RIDUZIONE

PROTOCOLLO DI STUDIO
QPART (Quantitative pilomotor axon reflex test)

- Fenilefrina 1% per ionoforesi (0.5 mA per 5’)
- Applicazione calco in silicone (10’’)
- Applicazione di toner per aumentare il contrasto
- Scansione del calco
- Analisi quantitativa


Axon reflex region
Direct region

Siepman T et al., Arch Neurol. 2012;69(11):1488-1492.

RISULTATI NELLO STUDIO DI VALIDAZIONE

Assenza di risposta per ionoforesi con soluzione salina

Assenza di differenze side-to-side in termini di

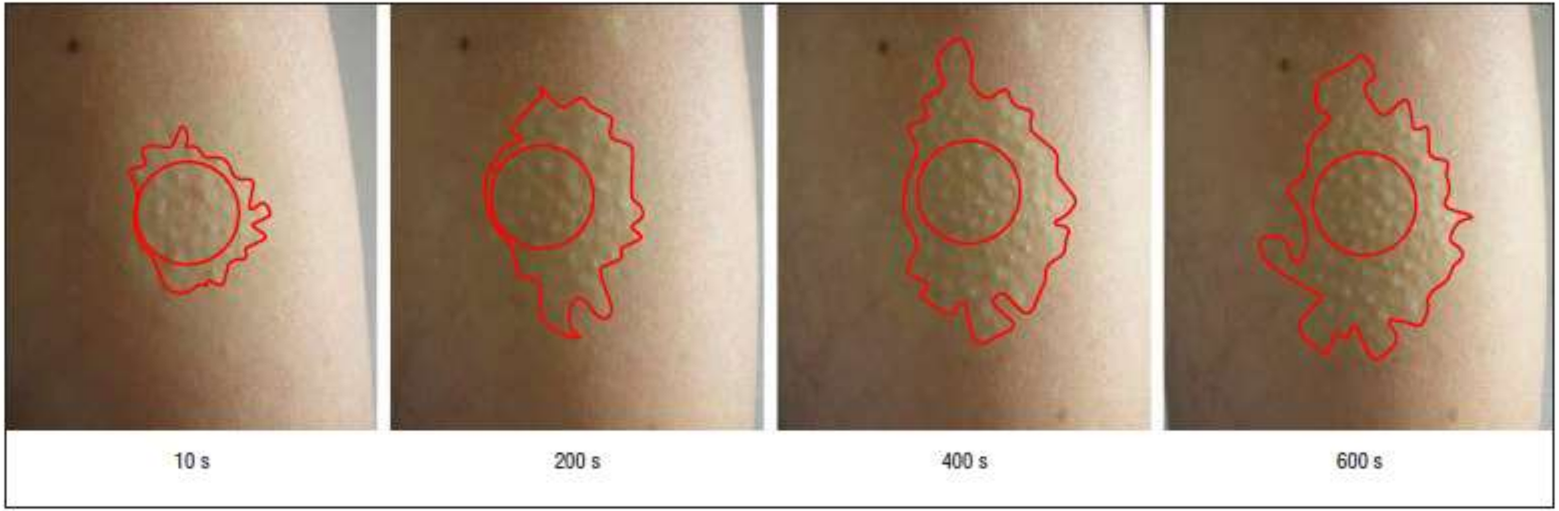
1) denistà di impronte nell'area di stimolazione diretta e riflessa
2) Estensione dell'area di piloerezione riflessa nella zona circostante l'area stimolata

	Area stimolata dx	**Area stimolata sx**	**Riflesso dx**	**Riflesso sx**
Densità impronte	13.4 ± 2.7	15.0 + 2.0	66.0 + 13.9	62.0 + 11.3
Area attivazione (cm^2)	-	-	51.0 + 3.2	51.5 + 3.2

RISULTATI NELLO STUDIO DI VALIDAZIONE

Latenza risposta diretta massimale 10 secondi

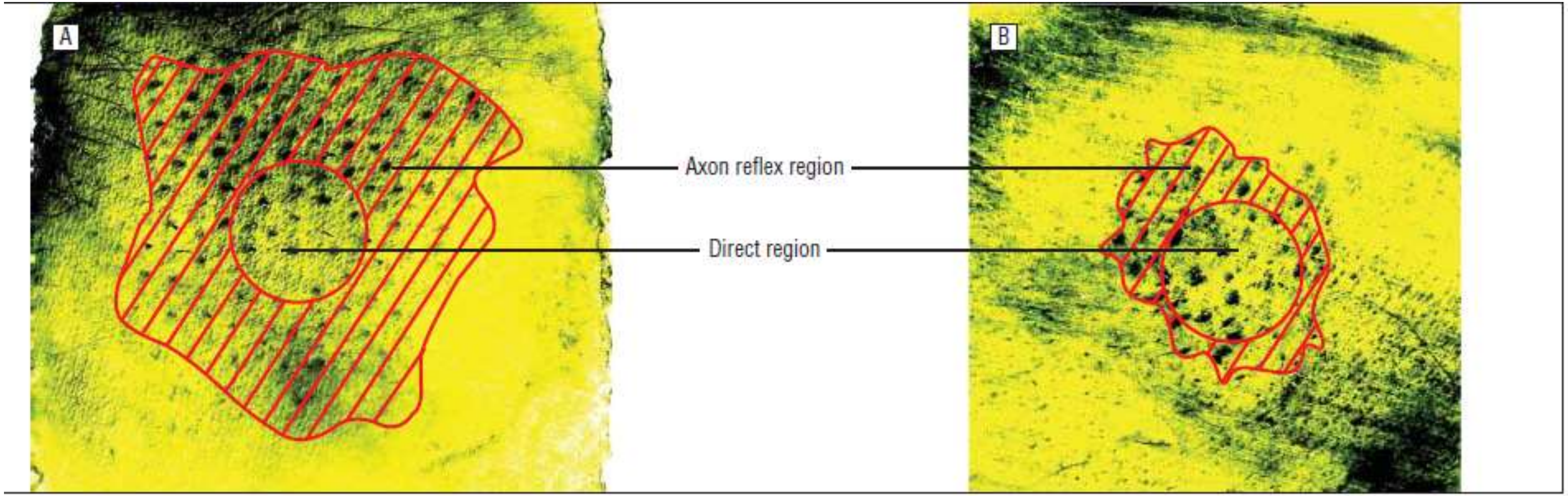
Latenza risposta riflessa massimale 600 secondi


10 s
200 s
400 s
600 s

RISULTATI NELLO STUDIO DI VALIDAZIONE

Pretrattamento con gel di lidocaina

1) Assenza di differenze nella reazione diretta
2) Marcata riduzione della risposta riflessa (neuromediata)


A
B
Axon reflex region
Direct region

QPART è l’unico test validato per la quantizzazione della funzione pilomotoria.

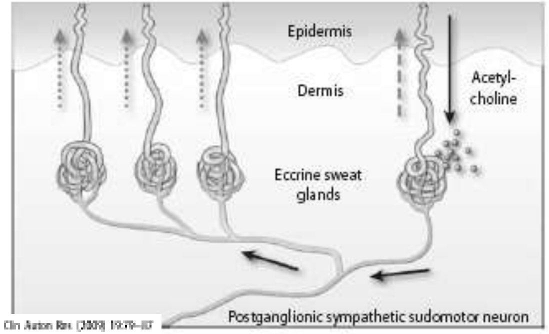
ma…

È stato testato solo in piccolo popolazioni di pazienti e mancano dati normative su casistiche estese

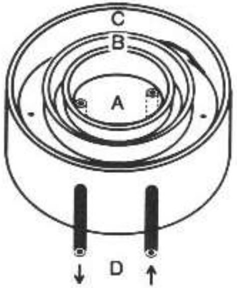
Stati emotivi e una temperature ambientale non controllata possono condizionare il test

La Giunzione sudomotoria

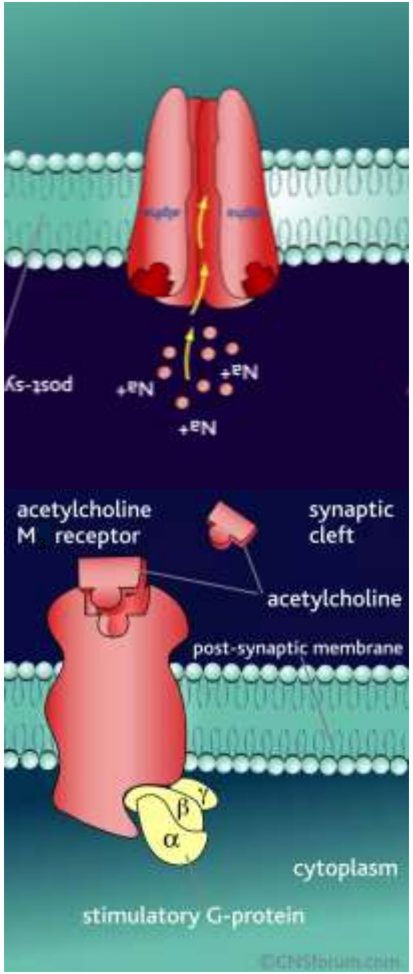
Quantitative sudomotor axon-reflex test - QSART


Epidermis
Dermis
Acetyl-choline
Eccrine sweat glands
Postganglionic sympathetic sudomotor neuron

Clin Auton Res (2009) 19:79–87

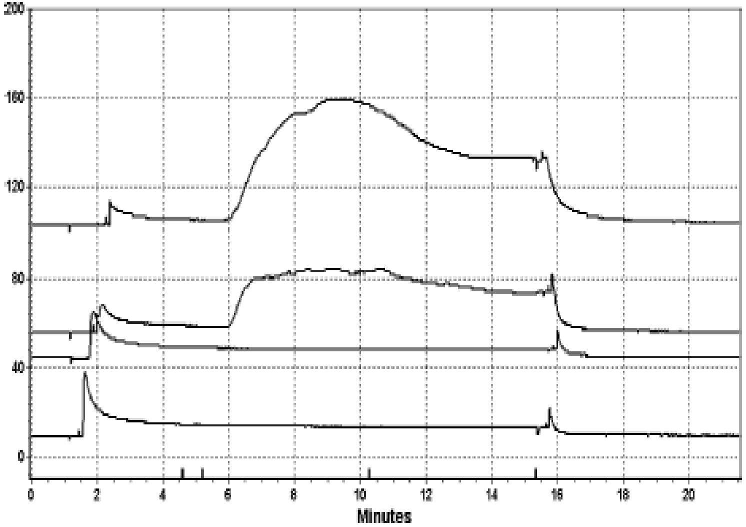


Ach per ionoforesi


Na+
Na+
Na+
acetylcholine M$_3$ receptor
synaptic cleft
acetylcholine
post-synaptic membrane
β
γ
α
cytoplasm
stimulatory G-protein
©CNSforum.com

QSART - risultati

Misurazione delle variazioni di umidità nel tempo



P.A. Low / Clinical Neurophysiology 115 (2004) 1506–1513

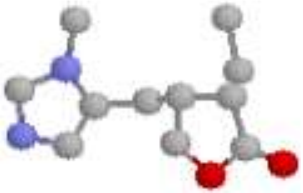
Parametri

Area sotto la curva

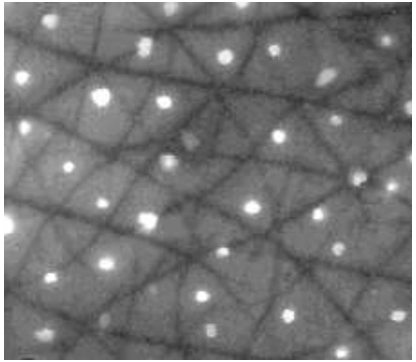
Massima produzione

Latenza

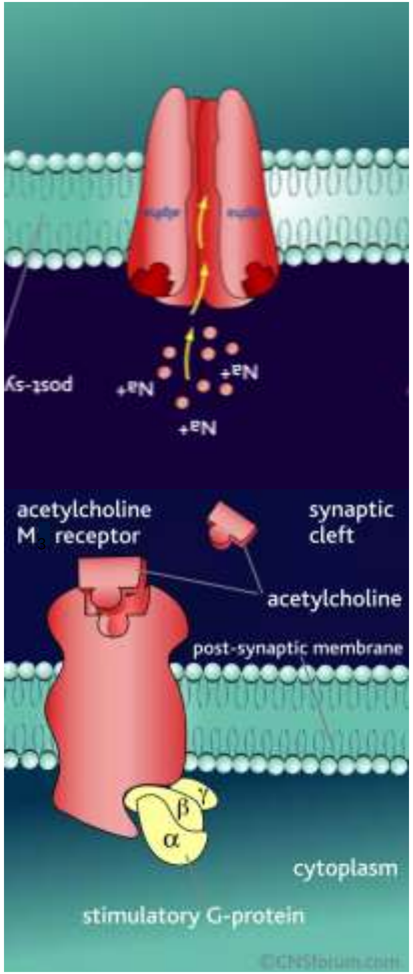
Silastic imprint test - SIT



Pilocarpina per ionoforesi



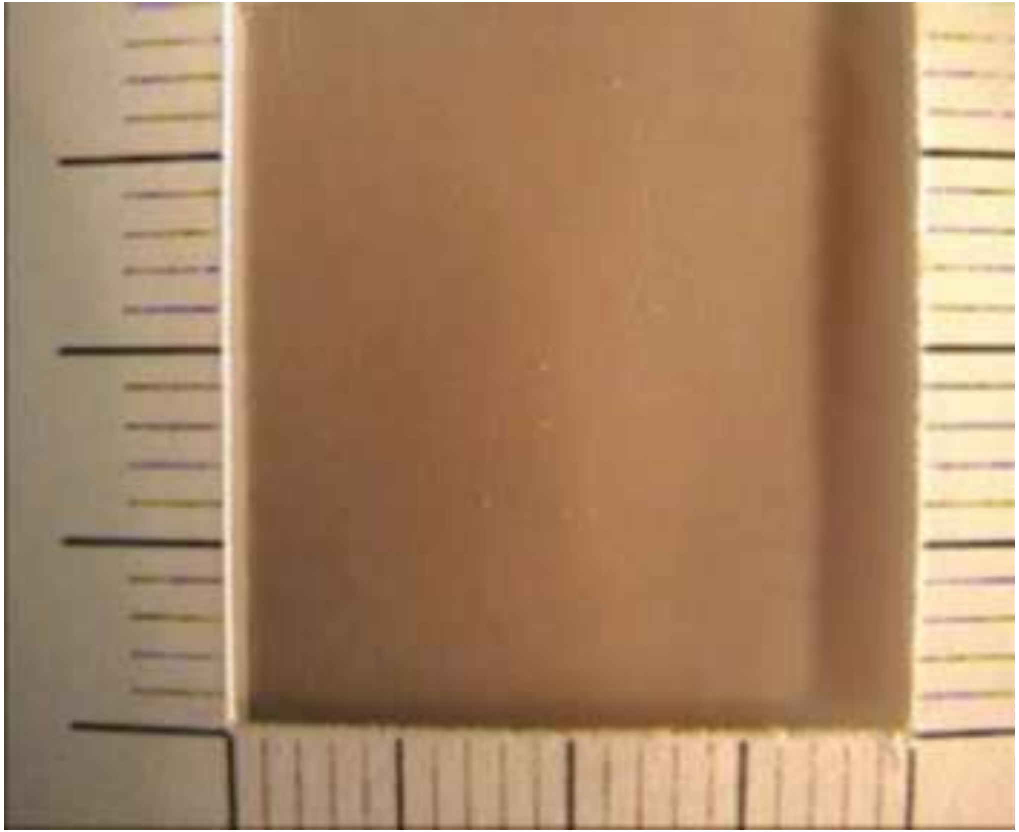
Valutazione distribuzione e densità delle ghiandole attivate

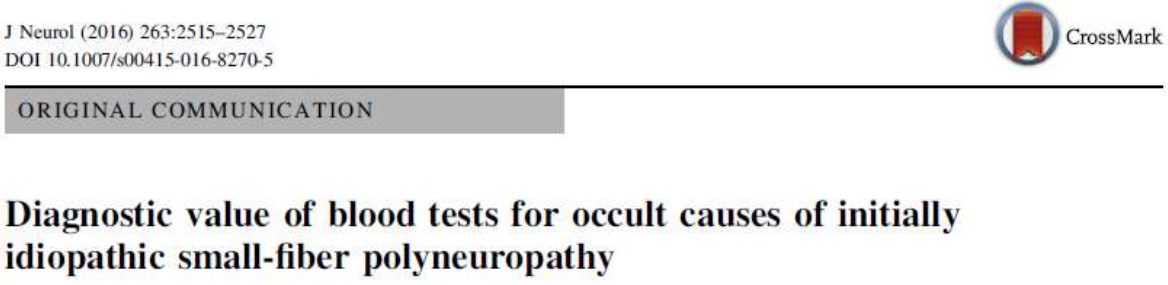

acetylcholine
M3 receptor
synaptic
cleft
acetylcholine
post-synaptic membrane
β
γ
α
cytoplasm
stimulatory G-protein
©CNSforum.com

Dynmic sweat test

DST - PARAMETRI VALUTATI

- **1. Numero di ghiandole attivate per cm^2**
- **2. Sudore prodotto per ghiandola per minuto (nl/min)**
- **3. Sudore prodotto per cm^2 per minuto**





J Neurol (2016) 263:2515–2527
DOI 10.1007/s00415-016-8270-5

CrossMark

ORIGINAL COMMUNICATION

Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy

Magdalena Lang[1] · Roi Treister[1] · Anne Louise Oaklanc

- 213 pazienti con diagnosi di sfn idiopatica definita

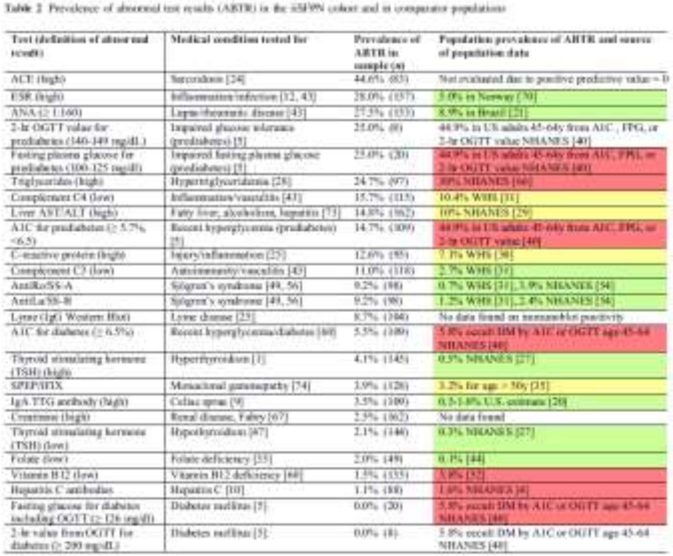


Table 2 Prevalence of abnormal test results (ABTR) in the iSFPN cohort and in comparator populations

Test (definition of abnormal result)	Medical condition tested for	Prevalence of ABTR in sample (n)	Population prevalence of ABTR and source of population data
ACE (high)	Sarcoidosis [24]	44.6% (83)	Not evaluated due to positive predictive value = 0
ESR (high)	Inflammation/infection [12, 43]	28.0% (157)	5.0% in Norway [70]
ANA (≥ 1:160)	Lupus/rheumatic disease [43]	27.3% (133)	8.9% in Brazil [21]
2-hr OGTT value for prediabetes (140-199 mg/dL)	Impaired glucose tolerance (prediabetes) [5]	25.0% (8)	44.9% in US adults 45-64y from A1C, FPG, or 2-hr OGTT value NHANES [40]
Fasting plasma glucose for prediabetes (100-125 mg/dl)	Impaired fasting plasma glucose (prediabetes) [5]	25.0% (20)	44.9% in US adults 45-64y from A1C, FPG, or 2-hr OGTT value NHANES [40]
Triglycerides (high)	Hypertriglyceridemia [28]	24.7% (97)	30% NHANES [66]
Complement C4 (low)	Inflammation/vasculitis [43]	15.7% (115)	10.4% WHS [31]
Liver AST/ALT (high)	Fatty liver, alcoholism, hepatitis [73]	14.8% (162)	10% NHANES [29]
A1C for prediabetes (≥ 5.7%, <6.5)	Recent hyperglycemia (prediabetes) [5]	14.7% (109)	44.9% in US adults 45-64y from A1C, FPG, or 2-hr OGTT value [40]
C-reactive protein (high)	Injury/inflammation [25]	12.6% (95)	7.1% WHS [38]
Complement C3 (low)	Autoimmunity/vasculitis [43]	11.0% (118)	2.7% WHS [31]
Anti-Ro/SS-A	Sjögren's syndrome [49, 56]	9.2% (98)	0.7% WHS [31], 3.9% NHANES [54]
Anti-La/SS-B	Sjögren's syndrome [49, 56]	9.2% (98)	1.2% WHS [31], 2.4% NHANES [54]
Lyme (IgG Western Blot)	Lyme disease [23]	8.7% (104)	No data found on immunoblot positivity
A1C for diabetes (≥ 6.5%)	Recent hyperglycemia/diabetes [60]	5.5% (109)	5.8% occult DM by A1C or OGTT age 45-64 NHANES [40]
Thyroid stimulating hormone (TSH) (high)	Hyperthyroidism [1]	4.1% (145)	0.5% NHANES [27]
SPEP/IFIX	Monoclonal gammopathy [74]	3.9% (126)	3.2% for age > 50y [35]
IgA TTG antibody (high)	Celiac sprue [9]	3.5% (109)	0.5-1.0% U.S. estimate [20]
Creatinine (high)	Renal disease, Fabry [67]	2.5% (162)	No data found
Thyroid stimulating hormone (TSH) (low)	Hypothyroidism [47]	2.1% (146)	0.3% NHANES [27]
Folate (low)	Folate deficiency [33]	2.0% (49)	0.1% [44]
Vitamin B12 (low)	Vitamin B12 deficiency [60]	1.5% (135)	3.0% [52]
Hepatitis C antibodies	Hepatitis C [10]	1.1% (88)	1.0% NHANES [4]
Fasting glucose for diabetes including OGTT (≥ 126 mg/dl)	Diabetes mellitus [5]	0.0% (20)	5.8% occult DM by A1C or OGTT age 45-64 NHANES [40]
2-hr value from OGTT for diabetes (≥ 200 mg/dL)	Diabetes mellitus [5]	0.0% (8)	5.8% occult DM by A1C or OGTT age 45-64 NHANES [40]

Prevalenza nella popolazione generale vs. prevalenza di test positivi nella popolazione di iSFN

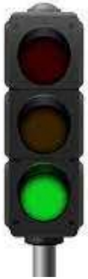
TEST	DISEASE	PERCENT OF POSITIVE TEST IN STUDY POPULATION	PREVALENCE IN GENERAL POPULATION
ANA (≥ 1:160)	Lupus/rheumatic disease	27.5%	8.9%
AntiRo/SS-A AntiLa/SS-B	Sjogren’s syndrome	9.2% 9.2%	0.7% 1.2%
TSH (high)	Hyperthyroidism	4.1%	0.5%
TSH (low)	Hypothyroidism	2.1%	0.3%
IgA TTG antibody (high)	Celiac sprue	3.5%	0.5-1.0%

Prevalenza nella popolazione generale vs. prevalenza di test positivi nella popolazione di iSFN

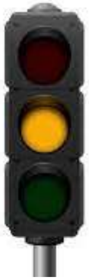
TEST	DISEASE	PERCENT OF POSITIVE TEST IN STUDY POPULATION	PREVALENCE IN GENERAL POPULATION
C-reactive protein (high)	Injury/inflammation	12.6%	7.1%
Complement C4 (low)	Inflammation/ vasculitis	15.7%	10.4%
Liver AST/ALT (high)	Fatty liver, alcoholism, hepatitis	14.8%	10%
SPEP/IFIX	Monoclonal gammopathy	3.9%	3.2%

Prevalenza nella popolazione generale vs. prevalenza di test positivi nella popolazione di iSFN

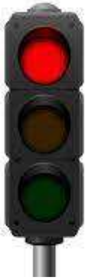
TEST	DISEASE	PERCENT OF POSITIVE TEST IN STUDY POPULATION	PREVALENCE IN GENERAL POPULATION
HbA1C (≥ 5.7%, <6.5)	prediabetes	14.7%	44.9%
HbA1C (≥ 6.5%)	diabetes	5.5%	5.8%
Vitamin B12 (low)	Vitamin B12 deficiency	1.5%	3.8%
Hepatitis C antibodies	Hepatitis C	1.1%	1.6%
ACE (high)	Sarcoidosis	44.6%	Not evaluated due to positive predictive value = 0



- ANA (≥ 1:160)
- AntiRo/SS-A AntiLa/SS-B
- TSH (high)
- TSH (low)
- IgA TTG antibody (high)



- C-reactive protein (high)
- Complement C4 (low)
- Liver AST/ALT (high)
- SPEP/IFIX



- HbA1C (⩾ 5.7%, <6.5)
- HbA1C (⩾ 6.5%)
- Vitamin B12 (low)
- Hepatitis C antibodies
- ACE (high)

Corso AINV.
La disautonomia nella pratica clinica: diagnosi e strategie terapeutiche

Grazie!