

EVENTO FORMATIVO
INTERREGIONALE SIIA

PIEMONTE - LIGURIA - VALLE D'AOSTA

TORINO
22.10.2022



REVIEW ARTICLE

IPO

A:

Syndrome of Supine Hypertension with Orthostatic Hypotension. A Nightmare for Physicians

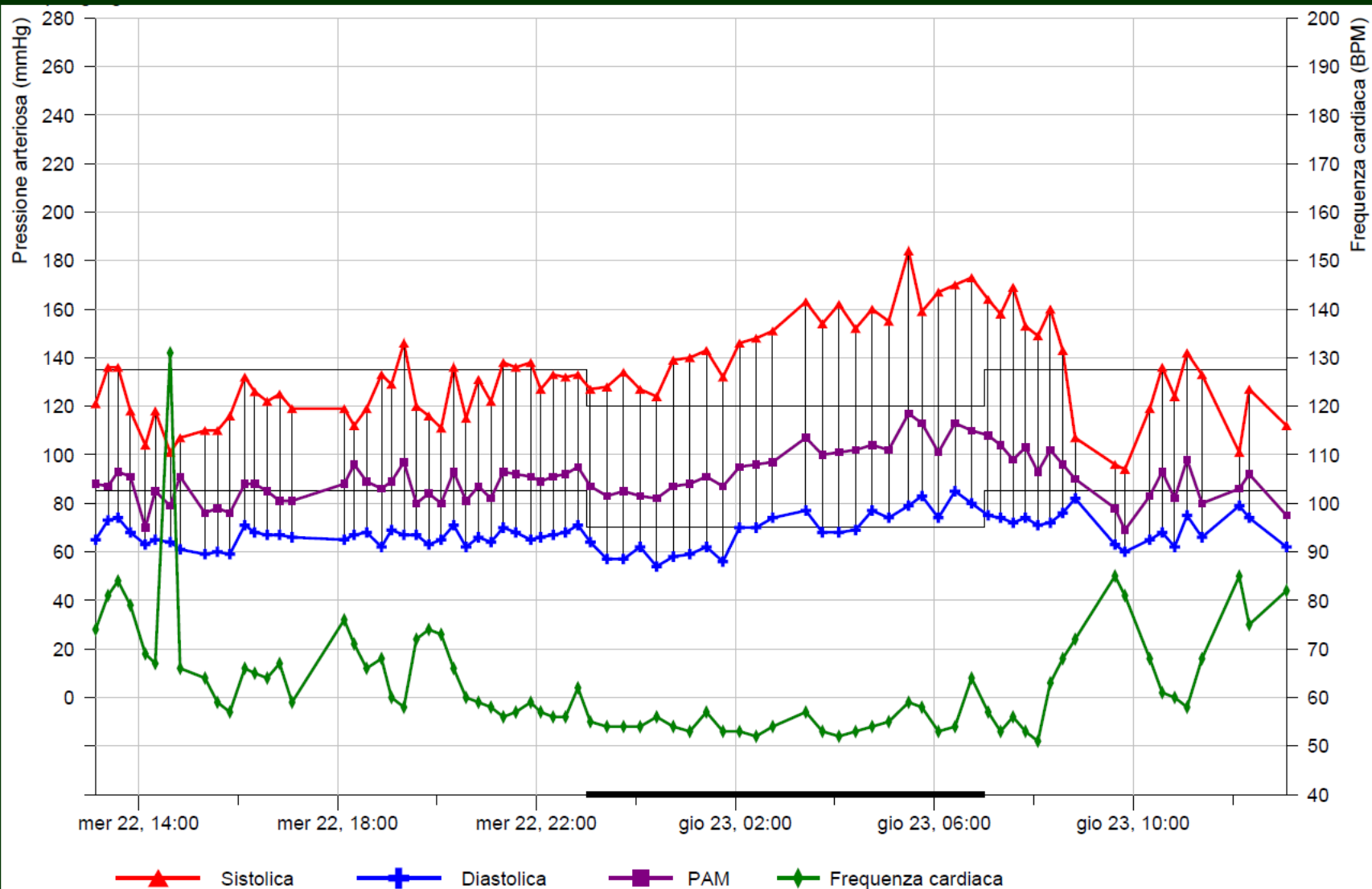
AAMIR AHMED, BS¹, BLAIR GRUBB, MD, FACC², LIAQAT ZAMAN, MD, FACC, FHRS¹ and KHALIL KANJWAL, MD, FACC, FHRS, CCDS¹

J Innov Card Rhythm Manag 7:2285,2016

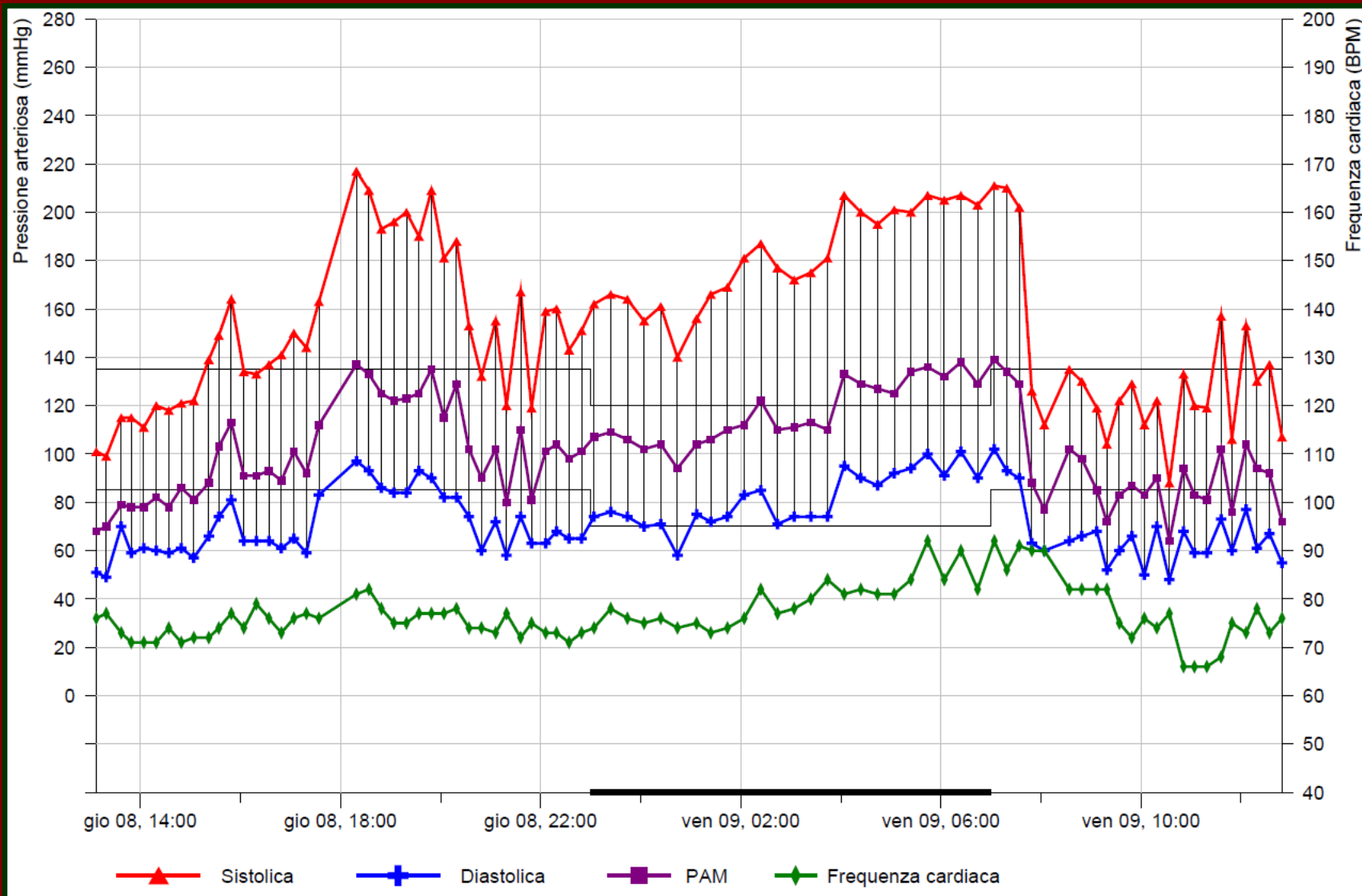
Clinica Medicina d' Urgenza

DI.M.I. – Università di Genova

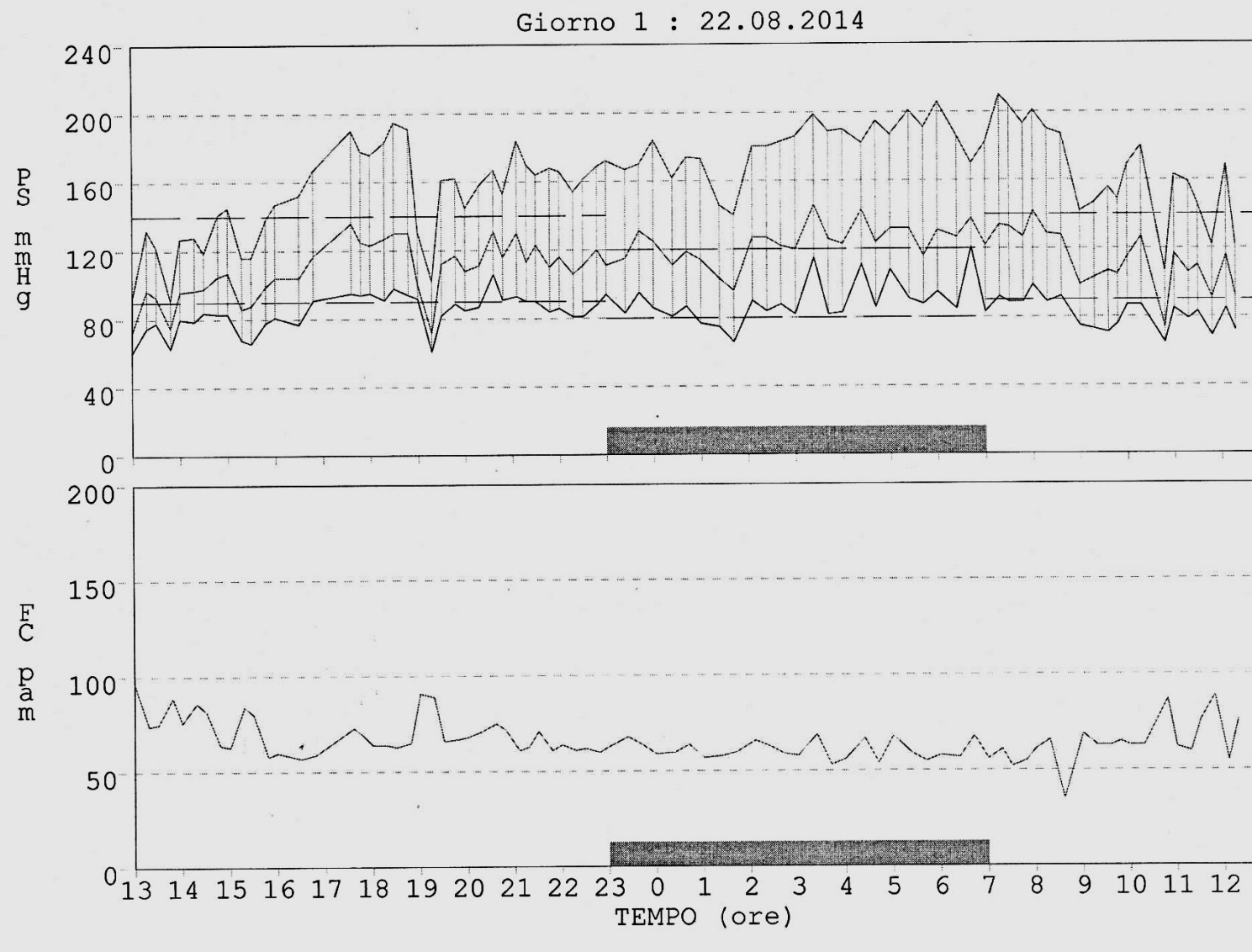
IRCCS Az. Ospedale Policlinico San Martino



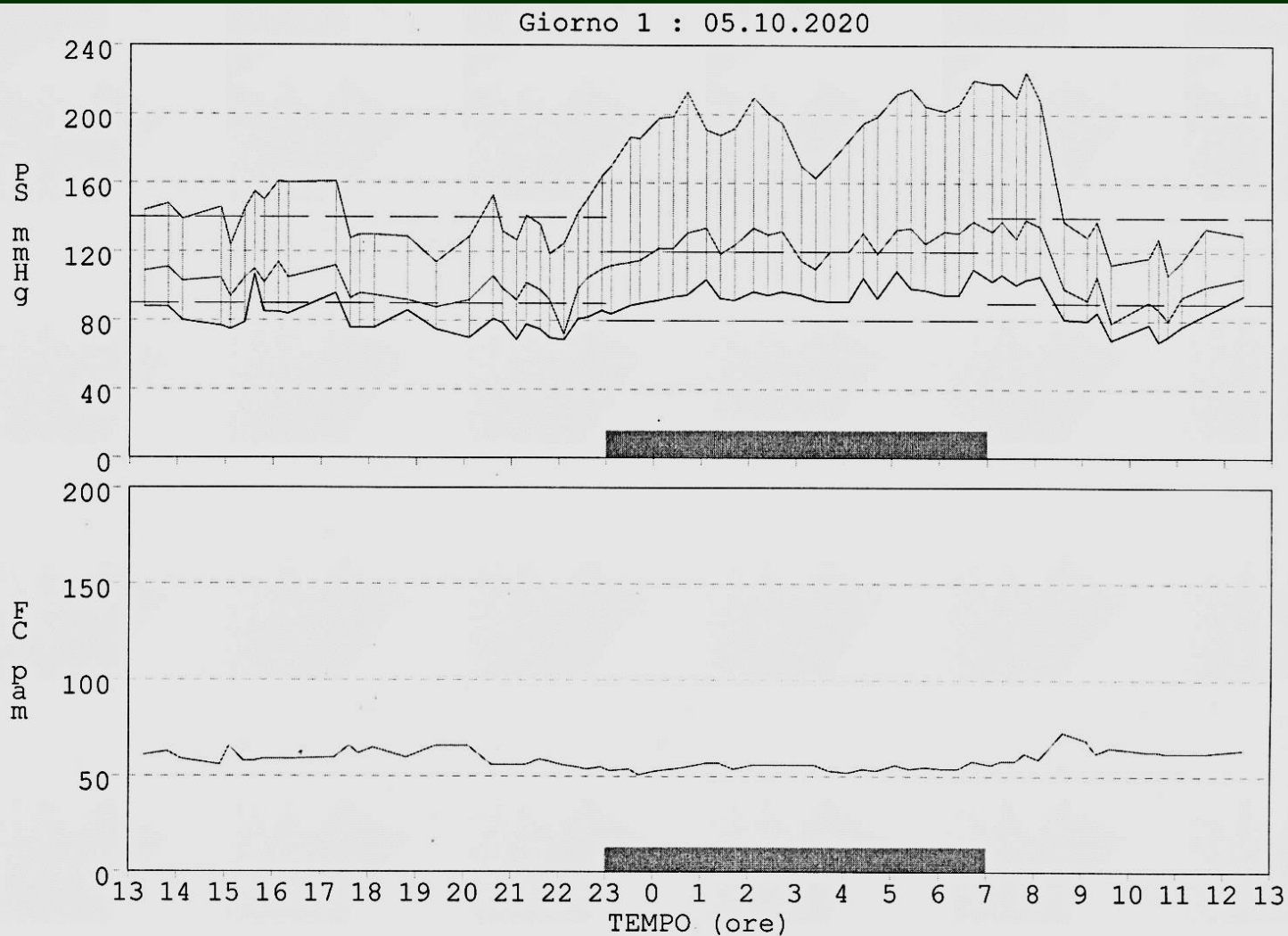
DA, uomo di 87 aa., pre-diabete, 2 TIA pregressi, tp. pressoria sospesa, dopo ABPM inizio Ramipril 2.5 mg h 21. Dopo 3 mesi ictus ischemico sottoposto a trombolisi.



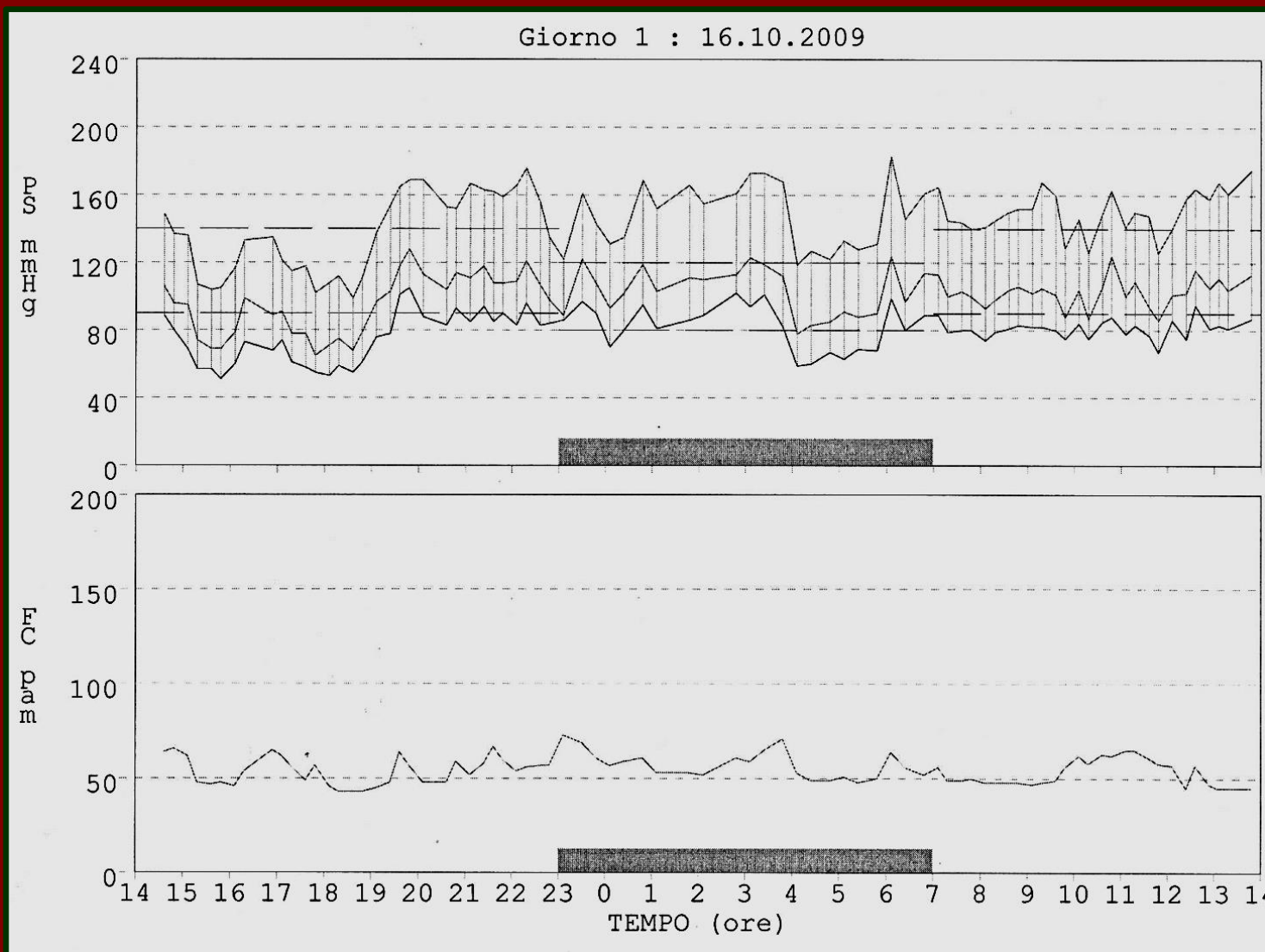
MF, uomo di 84 aa., diabetico, coronaropatico rivascolarizzato, in tp. con Valsartan qd/Carvedilolo bid/Levodopa-Benserazide tid/Doxazosina qd



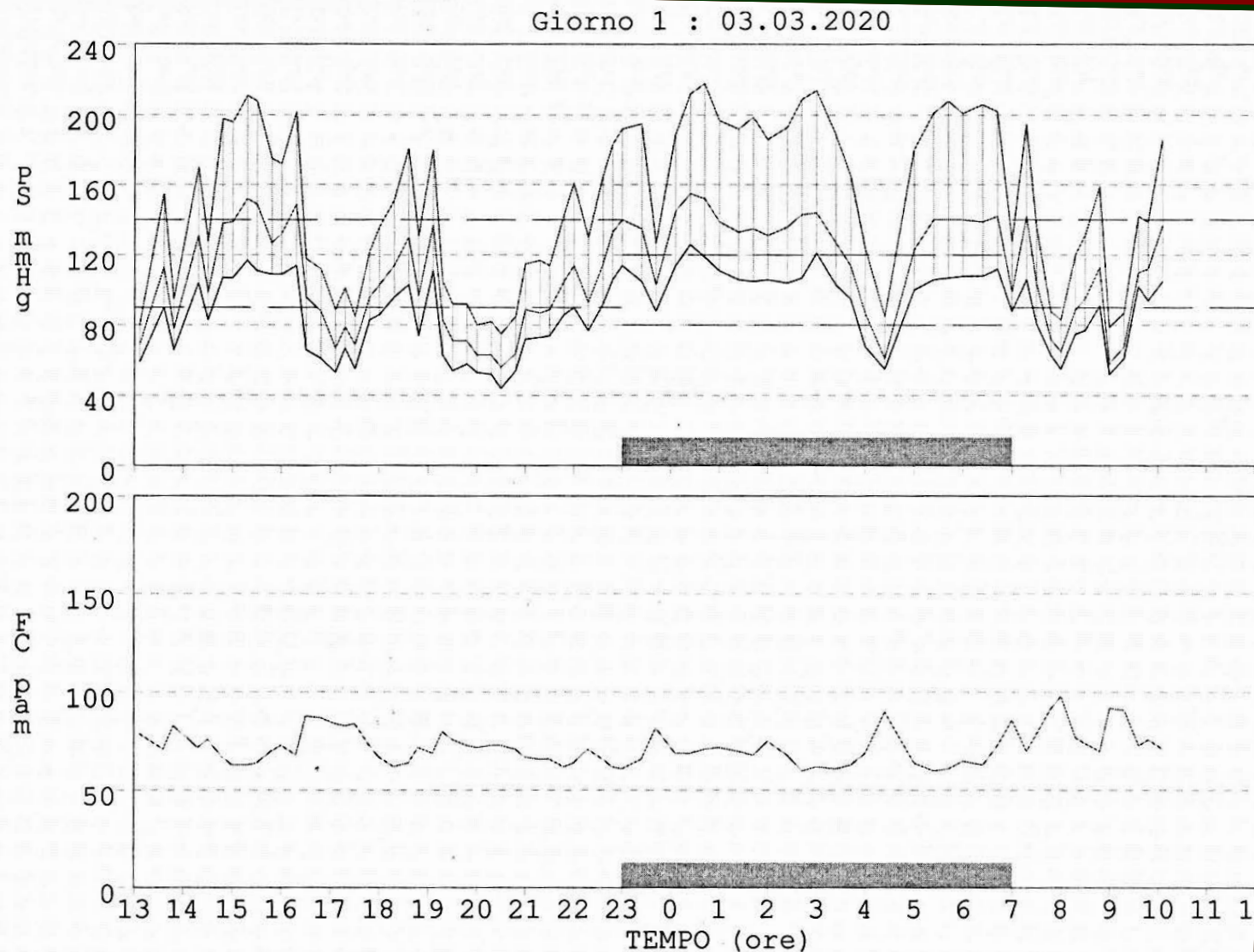
BBM, uomo di 79 aa., in tp. con Levodopa+Benserazide tid/altri farmaci non ipotensivi.



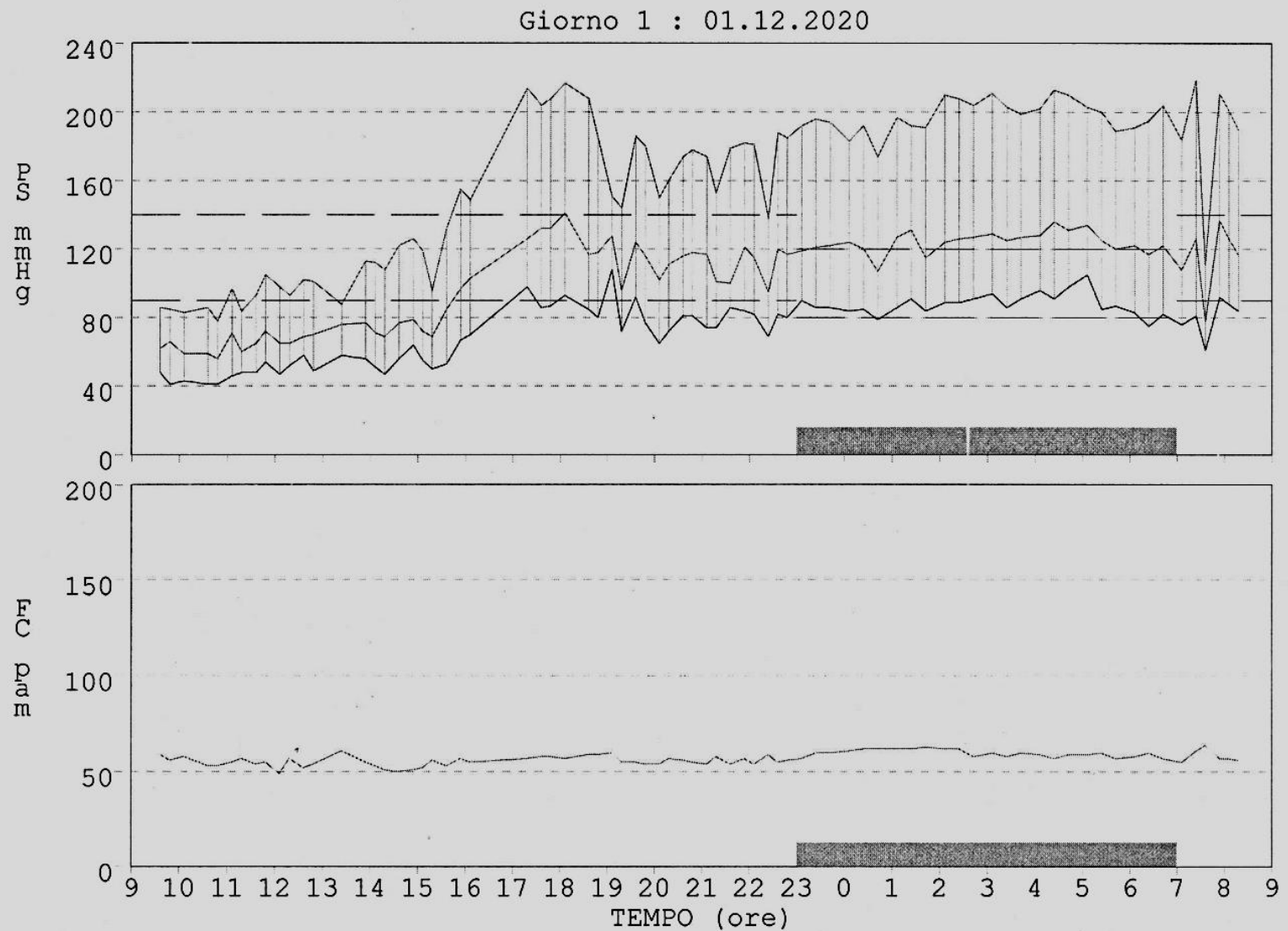
DR, uomo di 78 aa. con impianto di PEG-J per infusione continua di Duodopa, in tp. con Olmesartan qd, Bisoprololo qd, Escitalopram qd, altri farmaci non pressori



ME, uomo di 74 aa., in tp. con Levodopa+Benserazide bid/Pramipexolo tid/Candesartan bid/Atenololo qd, altri farmaci non pressori. Progresso IMA. 6 aa. dopo STEMI. 8 aa. dopo TIA.



GMA, donna di 70 aa. in tp. con Levodopa+Benserazide qid/Selegilina qd/Bisoprololo qd/ASA qd. Diagnosi successiva di possibile MSA per scarsa risposta alla Levodopa.



**MP, donna di 80 aa. in tp. con Levodopa+Benserazide bid/Selegilina bid/Nebivololo qd/
altri farmaci non pressori**



Machine learning applied to ambulatory blood pressure monitoring: a new tool to diagnose autonomic failure?

Fabrizio Vallelonga¹ · G. Sobrero¹ · A. Merola³ · M. Valente¹ · M. Giudici¹ · C. Di Stefano¹ · V. Milazzo¹ · J. Burrello¹ · A. Burrello⁴ · F. Veglio¹ · A. Romagnolo² · S. Maule¹

Review

J. Hypertens. 37:1102,2019

Diagnostic and therapeutical management of supine hypertension in autonomic failure: a review of the literature

Fabrizio Vallelonga and Simona Maule

Detection of orthostatic hypotension with ambulatory blood pressure monitoring in parkinson's disease

Fabrizio Vallelonga¹ · Alberto Romagnolo² · Aristide Merola³ · Gabriele Sobrero¹ · Cristina Di Stefano¹ · Valeria Milazzo¹ · Jacopo Burrello¹ · Alessio Burrello⁴ · Maurizio Zibetti² · Alberto Milan¹ · Franco Veglio¹ · Simona Maule¹



Blood pressure circadian rhythm alterations in alpha-synucleinopathies

Fabrizio Vallelonga¹ · Cristina Di Stefano¹ · Aristide Merola² · Alberto Romagnolo³ · Gabriele Sobrero¹ · Valeria Milazzo¹ · Alessio Burrello⁴ · Jacopo Burrello¹ · Maurizio Zibetti³ · Franco Veglio¹ · Simona Maule¹

Original Article

J. Hypertens. 38:289,2020

Cardiac organ damage in patients with Parkinson's disease and reverse dipping

Cristina Di Stefano^a, Gabriele Sobrero^a, Valeria Milazzo^a, Fabrizio Vallelonga^a, Alberto Romagnolo^b, Maurizio Zibetti^b, Alberto Milan^a, Franco Veglio^a, and Simona Maule^a

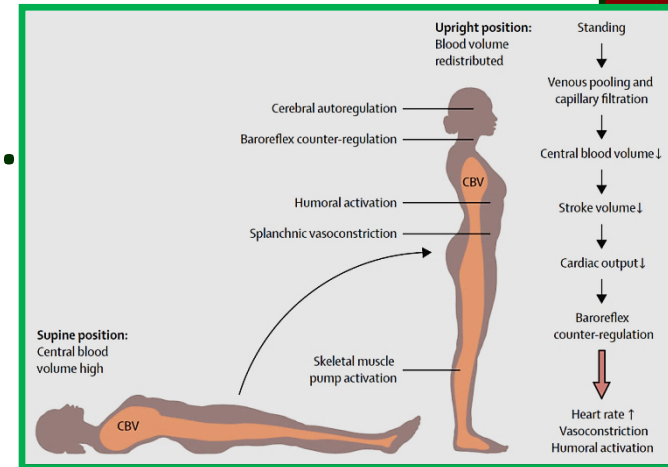


Treatment of supine hypertension in autonomic failure: a case series

Cristina Di Stefano¹ · Simona Maule¹

IPOENSIONE ORTOSTATICA: DEFINIZIONE

- Dopo 5 min. di posizione supina ed assunzione della posizione in piedi calo della PAS ≥ 20 mmHg (se il pz. è iperteso ≥ 30 mmHg) e/o della PAD ≥ 10 mmHg
- Rilevazioni pressorie dopo 1 e 3 min.
- Valutazione risposta FC
- Nel caso di valutazione seduto/in piedi calo significativo di PAS ≥ 15 mmHg e/o della PAD ≥ 7 mmHg



SINTOMI IPOTENSIONE ORTOSTATICA

- «Testa vuota, capogiri, vertigini, intontimento»
- Lipotimia e sincope
- Astenia
- Vista offuscata
- Alterazione cognitiva
- Dolore collo e spalle («coat hanger headache»)
- Dolore toracico
- Dispnea (platipnea)

RISPOSTA DELLA FC ALL' ORTOSTATISMO

Orthostatic decrease in blood pressure
(Decrease of 20/10 mm Hg within 3 minutes standing or head-up tilt)

Appropriate heart rate increase
(delta HR / delta SBP ratio ≥ 0.5)^a

Volume depletion

- Bleeding
- Gastrointestinal losses
- Renal losses
- Adrenal insufficiency

Vasodilating drugs

Venomotor incompetence

Systemic vasodilation states

- Sepsis

Inappropriate heart rate response
(delta HR / delta SBP ratio < 0.5)^a

Negative chronotropic drugs

Severe cardiac conduction defects

Autonomic failure (neurogenic orthostatic hypotension)

- Peripheral autonomic neuropathies
- Acute autonomic gangliopathy (autoimmune, paraneoplastic)

- Synucleinopathies (Parkinson disease, multiple systems atrophy, Lewy body dementia, pure autonomic failure)

^aDelta HR/delta SBP ratio = Rapporto tra la modifica della frequenza cardiaca e la modifica della PA sistolica all' ortostatismo

EZIOLOGIA NEUROPATIA AUTONOMICA PERIFERICA

Diabetes mellitus

Amyloidosis

AA (secondary) amyloidosis

AL (light chain, primary) amyloidosis

Transthyretin and other hereditary forms

Toxins

Heavy metals

Vincristine

Paclitaxel

Cisplatin

Thalidomide

Bortezomib

Infections

Human immunodeficiency virus

Chagas disease

Leprosy

Botulism

Diphtheria

Lyme disease

Syphilis

Autoimmune

Sjögren syndrome

Systemic lupus erythematosus

Mixed connective tissue disease

Sarcoidosis

Acute inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyneuropathy

Hereditary

Hereditary peripheral and autonomic neuropathy

Fabry disease

Allgrove syndrome

Paraneoplastic

Metabolic

Renal failure

Hypothyroidism

Vitamin B₁₂ deficiency

Porphyria

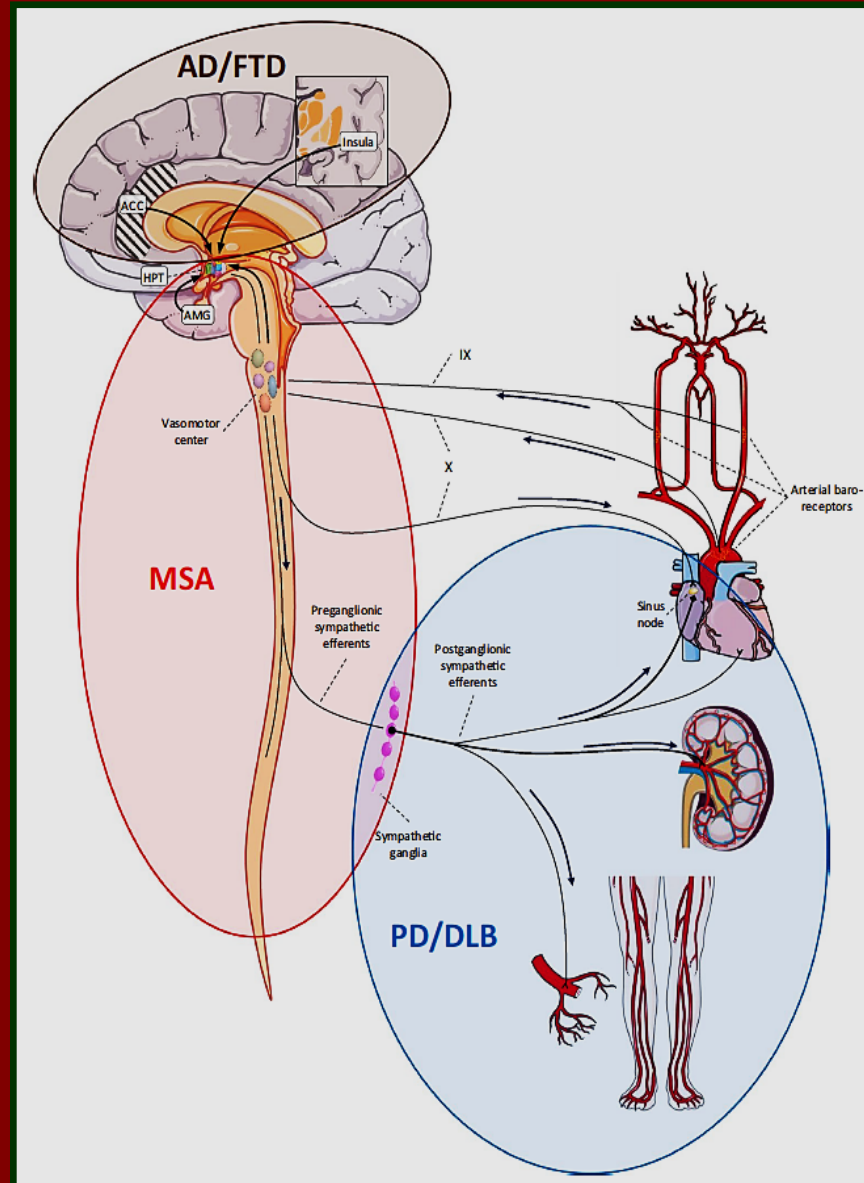
ALFA-SINUCLEINOPATIE

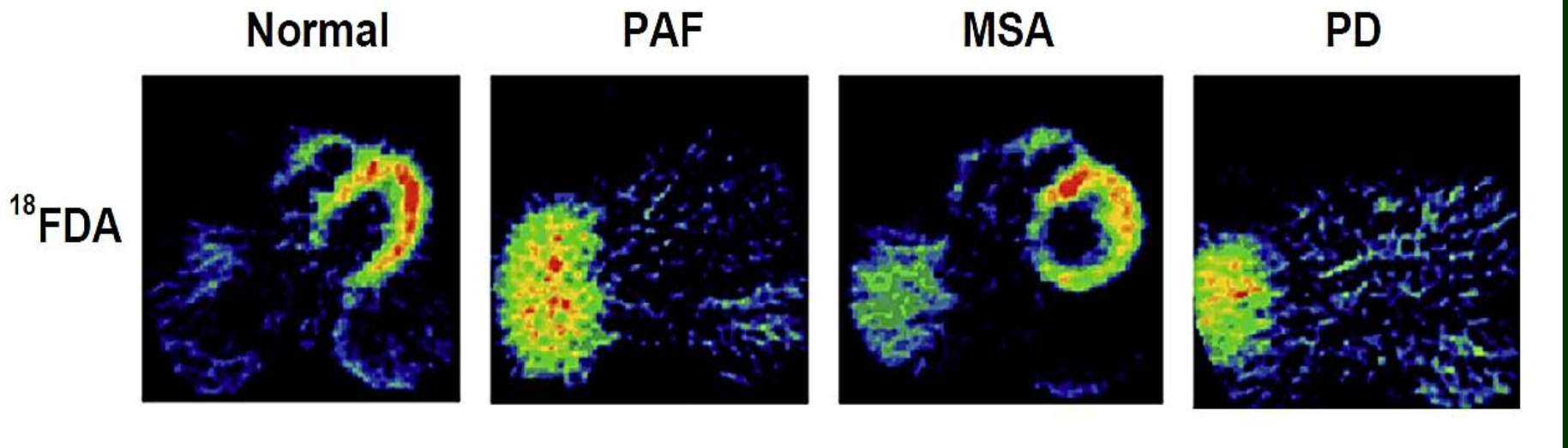
	MSA	PD	DLB	PAF
Motor features	Parkinsonism and/or cerebellar dysfunction (MSA-P o MSA-C)	Parkinsonism	Parkinsonism	None
Asymmetry	Mild	Prominent	Prominent	Not applicable
Autonomic features*	Early and severe	Variable onset and severity	Variable onset and severity. Typically more severe than PD	Presenting and cardinal feature
Sudomotor dysfunction	Regional. Proximal $\geq$ distal	Distal > proximal	Distal > proximal	Distal > proximal
Olfactory loss	No	Prominent	Prominent	Prominent
Stridor	Yes	No	No	None
Hallucinations	Rare	Late	Early	None
Cardiac PET scan	Normal	Abnormal	Abnormal	Abnormal
Response to levodopa	May respond in early disease stages	Yes	Yes	Not applicable
Pathology	Glial cytoplasmic inclusions	Lewy body and Lewy neurites	Lewy body and Lewy neurites	Lewy body and Lewy neurites

*Ipotesione ortostatica, ipertensione clinostatica, stipsi, incontinenza fecale, disfunzione urinaria e sessuale

DLB = dementia with Lewy bodies; MSA = multiple system atrophy; PAF = pure autonomic failure; PD = Parkinson disease; PET = positron emission tomography.

SINUCLEINOPATIE: SEDI DI COINVOLGIMENTO





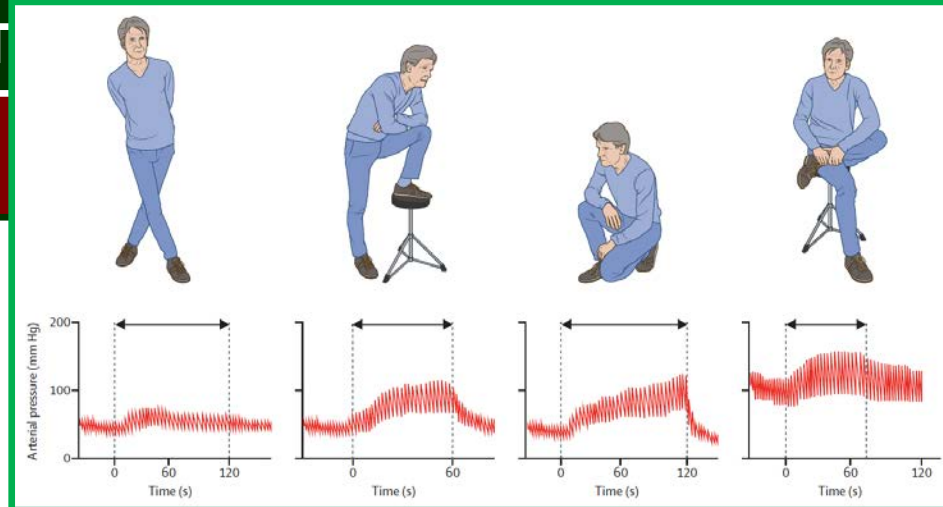
^{18}F -DOPAMINE PET SCANS CARDIACI IN SOGGETTO NORMALE, PZ. CON PURE AUTONOMIC FAILURE (PAF), PZ. CON MULTIPLE SYSTEM ATROPHY (MSA) E PZ. CON MORBO DI PARKINSON (PD)

FARMACI ANTI-PARKINSON: POSSIBILE EFFETTO IPOTENSIVO?

Drugs	Regimens	Type of clinical research	Sample characteristics	Result (mean $\pm$ SD)	Conclusion	Author (year)
Levodopa	200mg/d * 10 d	Case report	Sample size: N=1 Gender: female; Age: 70 y DD: 3 y	Systolic BP decline from 110-120 to 90 mmHg; OH	Controversial Need to be confirmed	Kondo, M. et al (2000) ¹
	62.5mg bid * 1w; 125-mg b.i.d. * 1w;	Double-blind, randomized, two-treatment cross-over trial	Sample size: N=17 (PD); N=17 (HC); Gender: N/A Age: 74.3 $\pm$ 0.9 y DD: N/A	OH was infrequently found in Parkinsonian patients (13%) and healthy subjects (6%) ; No significant difference.		Mehagnoul-Schipper, et al (2001) ²
	Not mentioned	Prospective observational research	Sample size: N=99 Gender: 72 male, 27 females; Age: 74 $\pm$ 7.8y; (range 52-88 y). DD: 7 $\pm$ 4.4 y (range 0-19 y)	The drop in blood pressure after orthostasis without levodopa medication reached on average 45.46 mmHg (SD = 23.76; SEM = 2.39), and the average drop after levodopa medication was 43.75 (SD = 17.88; SEM = 1.8). No significant difference.		Jost, W. H. et al (2020) ³
DAs						
Pramipexole	1.5mg /d* 6-15 m	Double-blind, randomized, Controlled trail	Sample size: N=261 Gender: N/A Age: N/A DD: early stage, N/A	2 patients developed drug-related postural hypotension	Need to be confirmed	Schapira, A. H. (2013) ⁴
	An ascending dose of 4.5 mg/day*9w	Multicenter Study Randomized Controlled Trial	Sample size: N=55 Gender: N/A Age: N/A DD: early stage, N/A	All subjects in both the pramipexole and the placebo groups experienced one or more episodes of asymptomatic OH and there was no significant difference between the pramipexole and the placebo groups		On Underlying Disease (PROUD) Hubble, J. P. (1995) ⁵

TRATTAMENTO NON FARMACOLOGICO DELL' IPOTENSIONE ORTO

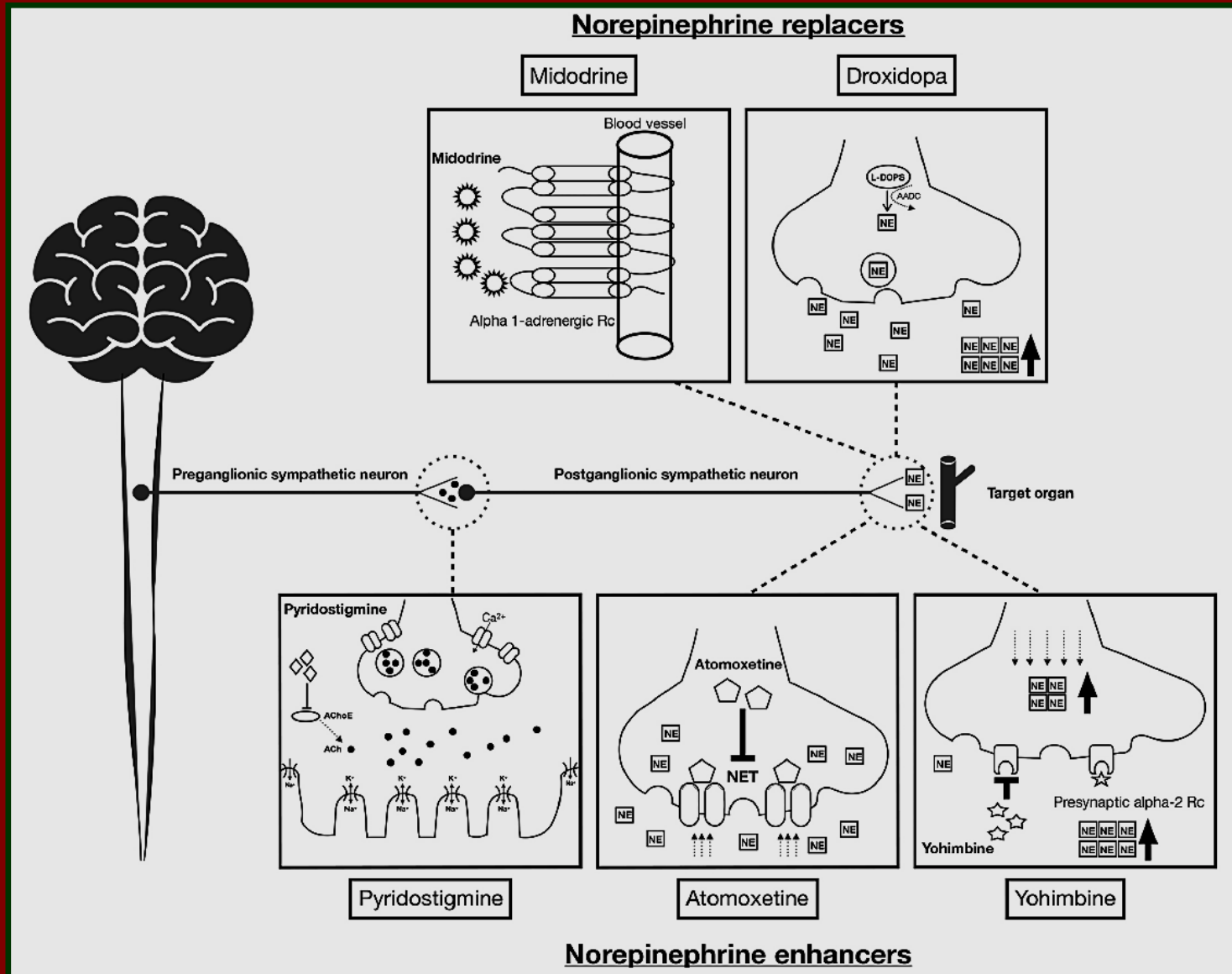
- Educazione e «counselling»
- Rivalutazione dei farmaci
- Manovre di contrasto
- Adeguato apporto d' acqua (2-3 L/die) ed eventuale assunzione rapida di un bolo (1/2 L in 2-3 min.)
- Pasti piccoli e frequenti a basso contenuto di carboidrati e senza alcolici
- Aumento dell' introito salino (sodiuria >150 mEq/24 h)
- Mantenimento di una buona attività fisica
- Sedia nel vano doccia
- Posizionamento nel letto
- Calze elastiche o, meglio, fascia addominale



TRATTAMENTO FARMACOLOGICO DELL' IPOTENSIONE ORTOSTATICA NEUROGENA

	Mechanism	Recommended dose	Side-effects	GRADE recommendation	FDA approval for orthostatic hypotension
Droxidopa ¹⁰¹	Short-acting synthetic norepinephrine precursor	100–600 mg 3 times a day (morning, midday, and 3–4 h before going to bed) or tailored to the patients' needs	Supine hypertension, headache, nausea, fatigue; use with caution in patients with congestive heart failure or chronic renal failure	Ila	Yes
Midodrine ¹⁰²	Short-acting direct α_1 -adrenergic receptor agonist	2.5–15 mg 2 or 3 times a day (morning, midday, and 3–4 h before going to bed or tailored to the patients' needs)	Supine hypertension, piloerection (goose bumps), itchy scalp, urinary retention; use with caution in patients with congestive heart failure or renal failure	Ila	Yes
Fludrocortisone ⁹⁶	Long-acting synthetic mineralocorticoid (volume expansion that increases sodium and water reabsorption)	0.05–0.2 mg once a day; no benefit with doses higher than 0.2 mg/day	Supine hypertension, hypokalaemia, renal failure, oedema, end organ damage; use with caution in patients with congestive heart failure	IIb	No
Acarbose ¹⁰³	Short-acting α -glycosidase inhibitor	50–150 mg before meals to prevent postprandial hypotension	Abdominal gas, bloating	IIc	No
Atomoxetine ⁹⁷	Short-acting norepinephrine reuptake inhibitor	10–18 mg twice a day	Supine hypertension, insomnia, irritability, decreased appetite	IIc	No
Pyridostigmine ^{98,99}	Short-acting acetylcholinesterase inhibitor	30–60 mg 2 or 3 times a day	Abdominal cramps, diarrhoea, sialorrhoea, excessive sweating, urinary incontinence	IIc	No
Evidence graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) recommendation. ¹⁰⁴					

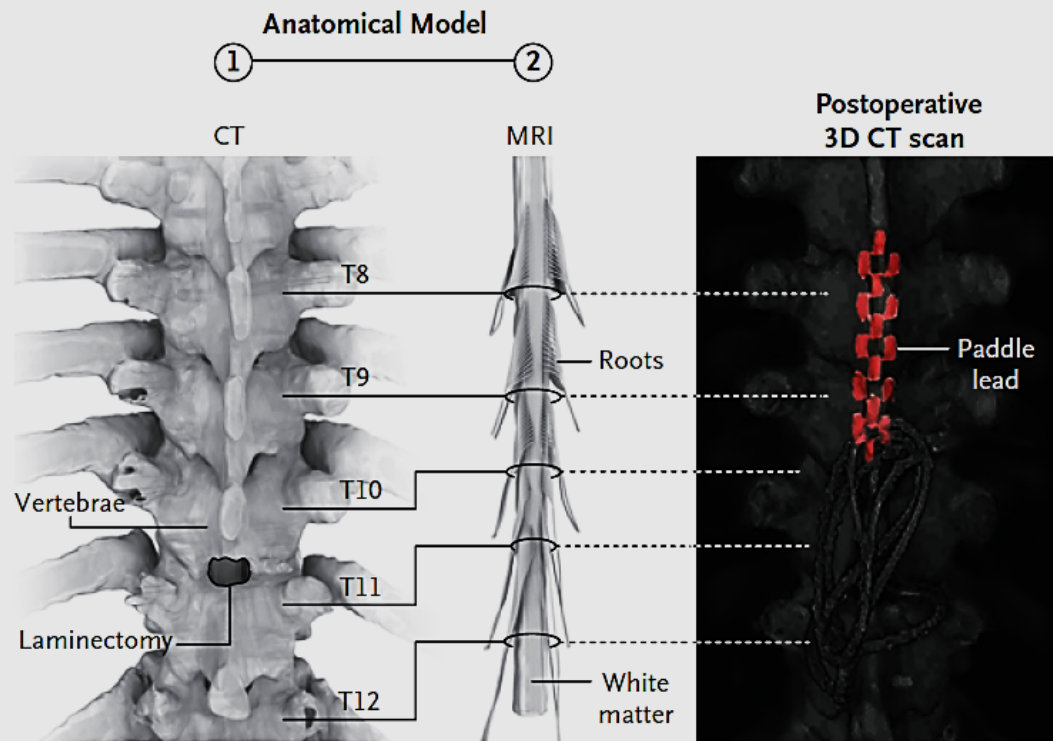
FARMACI PER L' AUMENTO DEL TONO SIMPATICO



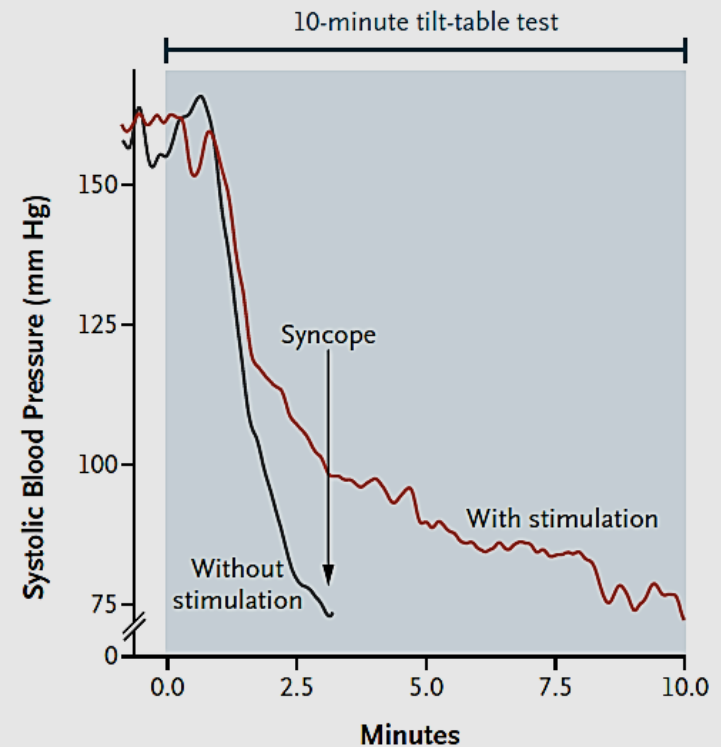
Implanted System for Orthostatic Hypotension in Multiple-System Atrophy

Jordan W. Squair, Ph.D., Maxime Berney, M.D., Mayte Castro Jimenez, M.D.,
Nicolas Hankov, M.Sc., Robin Demesmaeker, Ph.D., Suje Amir, M.Sc.,
Aurelie Paley, M.Sc., Sergio Hernandez-Charpak, M.Sc., Gregory Dumont, Ph.D.,
Leonie Asboth, Ph.D., Gilles Allenbach, M.D., Fabio Becce, M.D.,
Patrick Schoettker, M.D., Gregoire Wuerzner, M.D., Julien F. Bally, M.D.,
Grégoire Courtine, Ph.D., and Jocelyne Bloch, M.D.

A



B



TRATTAMENTO NON FARMACOLOGICO DELL' IPERTENSIONE CLINOSTATICA

IPERTENSIONE CLINOSTATICA = PAS $\geq$ 140 mmHg and/or PAD $\geq$ 90 mmHg, misurate dopo almeno 5 min in posizione supina. Spesso asintomatica ma può esacerbare l' ipotensione ortostatica mattutina per ipovolemia da diuresi pressoria notturna e correlarsi con il danno cardiaco e renale

Recommendations

Benefits/mechanisms

Nocturnal head-up tilt position [50] (~20 cm)	Reduction of night-time pressure natriuresis improvement of morning orthostatic tolerance
Small snack at bedtime [54]	Induction of postprandial hypotension
Drinking water mainly during daytime [55,57]	Osmopressor reflex during orthostatism
Reduce salt intake [29,57] – in patients with SH prevailing over OH	Reduction in plasma volume
Avoid daytime supine position [56]	Reduction of venous pooling
Avoid compression stockings in supine position	Reduction of venous pooling
Avoid under-recognized pressor agents [58,59,61,62]	Risk of severe hypertensive crisis and acute organ damage
Patients' education (awareness of BP changes in supine, sitting, and upright positions) [3]	Sitting position can decrease BP to normal ranges
Patients' education (awareness of timing and doses of antihypertensive drugs) [36]	Improvement of therapeutical compliance

BP, blood pressure; OH, orthostatic hypotension; SH, supine hypertension.

Vallelonga & Maule J Hypertens 37:1102,2019

TRATTAMENTO FARMACOLOGICO DELL' IPERTENSIONE CLINOSTATICA

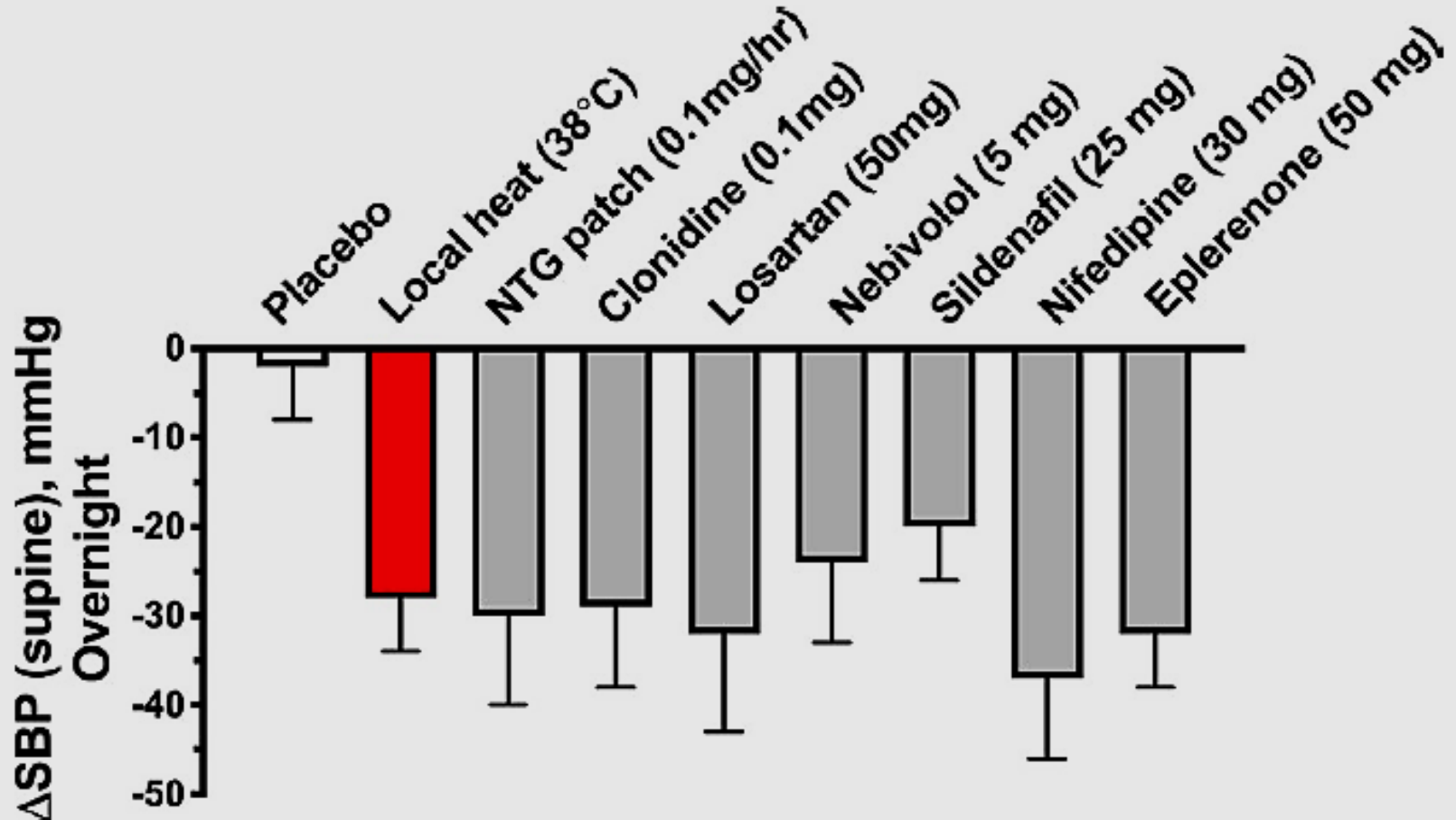
Medication (mechanism/class)	Typical dose	Half-life
Captopril (angiotensin-converting enzyme inhibitor) [26]	25 mg at bedtime	< 3 h [101]
Eplerenone (mineralocorticoid receptor antagonist) [25]	50 mg at bedtime	4–6 h [106]
Hydralazine (vasodilator; peripheral smooth-muscle relaxant) [44]	10–25 mg at bedtime	3–7 h [102]
Losartan (angiotensin II receptor antagonist, acting on AT1 receptor subtype) [103]	25–50 mg at bedtime	2 h (metabolite 6–9 h) ^a [99]
Nifedipine (calcium channel blocker) ^b [104]	30 mg at bedtime	2 h ^c [105]
Nitroglycerin patch (vasodilator) [44]	0.1 mg/h patch at bedtime (remove patch in morning)	3 min [100]
AT1 angiotensin type 1 receptor ^a Terminal half-life ^b Prolonged duration of hypotensive effect may worsen orthostatic hypotension in the morning [104] ^c Elimination half-life of immediate-release formulation		

Isaacson et al. Curr Neurol Neurosci Rep 21:18,2021

RECENTI ACQUISIZIONI PER IL TRATTAMENTO DELL' IPOTENSIONE ORTOSTATICA E DELL' IPERTENSIONE CLINOSTATICA

	Mechanism of action	Recommended dosage	Outcomes
Therapies for OH that do not worsen sHTN			
Pyridostigmine [55]	Cholinesterase inhibitor, facilitates autonomic ganglia neurotransmission	30–60 mg, orally, up to 3 times/ daytime	Improve OH without worsening supine hypertension
Automated inflatable abdominal binder [30••]	Target splanchnic venous pooling	servo-controlled venous compression (40 mmHg)	Ameliorates OH (as effective as midodrine) without worsening supine hypertension.
Therapies for nocturnal sHTN that do not improve daytime OH			
Clonidine [46]	Central alpha-2 agonist	0.1 mg, orally, with dinner	SBP decrease: 29 mmHg in MSA patients
Eplerenone [21•]	Mineralocorticoid receptor antagonist	50 mg, orally, at bedtime	SBP decrease: 32 mmHg
Sildenafil [19]	Phosphodiesterase inhibitor, potentiates nitric oxide	25 mg, orally, at bedtime	SBP decrease: 24 mmHg
Losartan [20]	Angiotensin II receptor antagonist	50 mg, orally, at bedtime	SBP decrease: 32 mmHg
Nifedipine [56]	Calcium channel blocker	10-30 mg short-acting, orally, at bedtime, or 30 mg ER	SBP decrease: 37 mm Hg, but increases nocturnal natriuresis
Nitroglycerin patch [9]	Vasodilator, nitric oxide donor	0.1 mg/h patch at bedtime, remove in the morning	SBP decrease: 36 mmHg
Therapies for nocturnal sHTN that can improve daytime OH			
Head-up and bed tilt [7•, 57]	Induce venous pooling below the level of the heart, reduce renal hyper-perfusion and reduce pressure diuresis	Head up bed tilting (10 degrees)	Effect on nocturnal supine SBP not systematically assessed Improves daytime upright SBP by 11 mmHg
Local passive heat [54••]	Peripheral vasodilation and blood redistribution	38 °C heating pad placed under the torso or a heated mattress	Nocturnal supine SBP decrease: 19–28 mmHg Improves daytime upright SBP by 19 mmHg

CONFRONTO TRA TRATTAMENTI DISPONIBILI PER IPERTENSIONE CLINOSTATICA

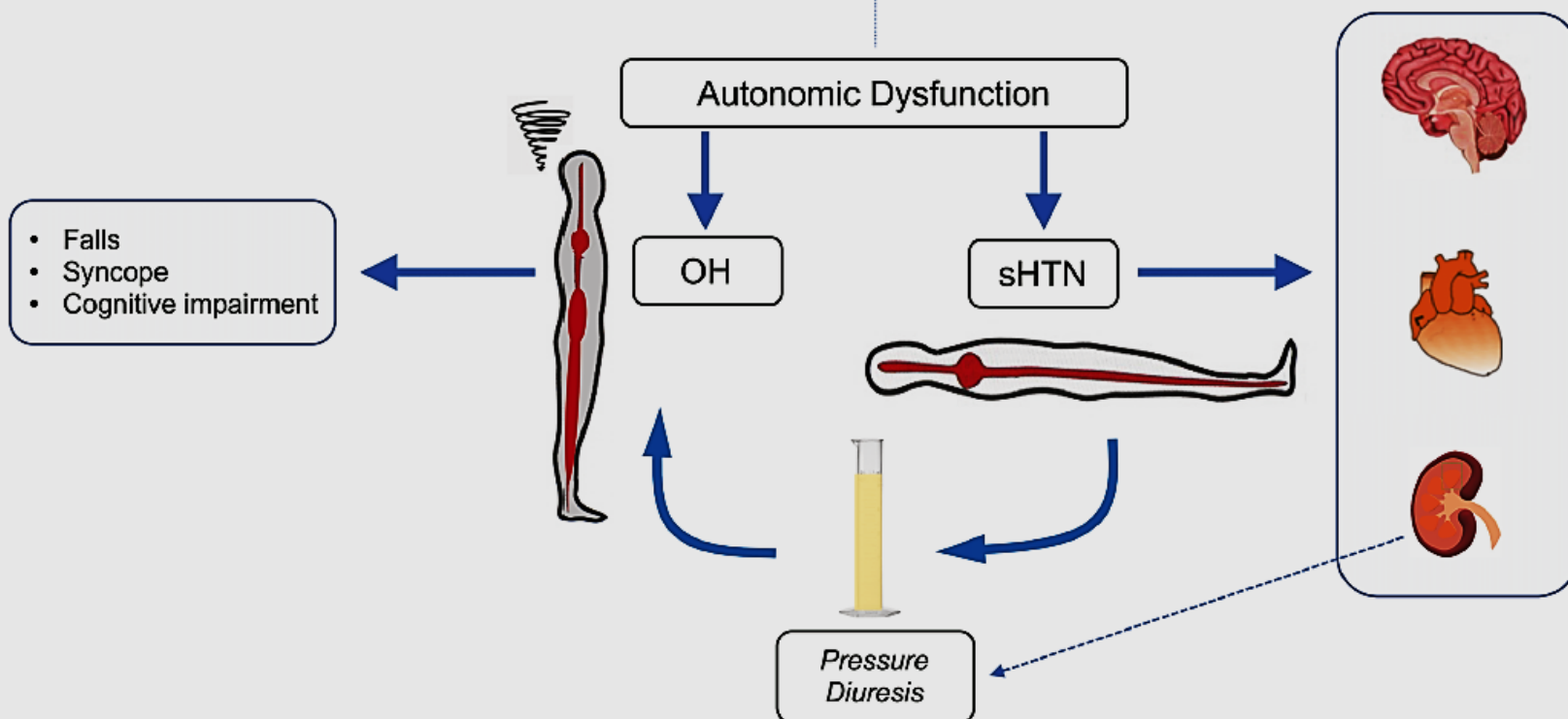


Pharmacologic Treatments

- Pyridostigmine

- Short acting antihypertensives at bedtime

End-Organ Damage



- Oral water bolus
- Abdominal binder

- Avoid supine posture during the day
- Carbohydrate-rich snack at bedtime
- Sleeping in HUT
- Local passive heat

Non-pharmacologic Treatments

CONCLUSIONI

- Nonostante il fatto che l'associazione tra ipotensione ortostatica ed ipertensione clinostatica sia nota da tempo, le modalità di approccio rimangono ancora non ben definite
- Il giudizio clinico deve basarsi su un'attenta valutazione dei pro e contro di una determinata scelta terapeutica in funzione della sua tollerabilità e degli aspetti prognostici
- La conoscenza approfondita delle opzioni non-farmacologiche e farmacologiche può aiutare in maniera significativa i pazienti



Vi ringrazio dell'attenzione

Genova, Porto Antico