



5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 4

**Emergencies in neurology: dealing effectively with
syncope and transient loss of consciousness (TLOC)
(Level 1)**

Orthostatic hypotension and falls

Alessandra Fanciulli
Innsbruck, Austria

Email: alessandra.fanciulli@i-med.ac.at



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Orthostatic hypotension and falls

Alessandra Fanciulli MD PhD

Department of Neurology, Medical University of Innsbruck - Austria

EAN 2019 - Oslo, June 29th 2019

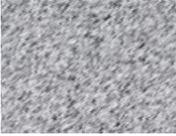
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I have no commercial conflicts of interest with the information presented herewith.



Reason for referral: SCHWINDEL



Janus-faced



Queuing at the post office



It's a matter of few seconds...



Reason for referral: SCHWINDEL

Mrs Doubtfire, 71-years old

Complains of vertigo, dizziness and blurred vision. Gastrointestinal infection until 3 days ago, lives alone and does not feel safe at home.

Comorbidities: diabetes, hypertension, depression.

Medications: insulin, lisinopril, escitalopram.

On status: ↓ deep tendon reflexes, distal numbness in the lower extremities.

Blood pressure: 120/75 mmHg.

Lab: blood sugar 99 mg/dL, Haemoglobin 11.9 g/dL, K+ 3.4 mmol/L, Na+ 137 mmol/L.

Mrs Doubtfire, 71-years old

Which is the most plausible cause of Mrs Doubtfire's complaints?

- a. Hypoglycaemia
- b. Anaemia
- c. Electrolytes imbalance
- d. Phobic vertigo
- e. Don't know...

Mrs Doubtfire, 71-years old

Which is the most plausible cause of Mrs Doubtfire's complaints?

- a. Hypoglycaemia
- b. Anaemia
- c. Electrolytes imbalance
- d. Phobic vertigo
- e. Don't know...**

5 minutes more for history taking...



„...today it is worse, but I've been feeling so for quite some months“



„It always happens when I stand or walk for a longer time....“

„Does it get better if you sit or lay down?“

„Yes“

Mrs Doubtfire, 71-years old

Supine blood pressure: 118/75 mmHg

Standing blood pressure: 89/64 mmHg, reports dizziness

Mrs Doubtfire, 71-years old

Which is the most plausible cause of Mrs Doubtfire's complaints?

- a. Hypoglycaemia
- b. Anaemia
- c. Electrolytes imbalance
- d. Phobic vertigo
- e. Don't know...
- f. Orthostatic hypotension**

Orthostatic hypotension (OH)

BP fall ≥ 20 mmHg systolic or ≥ 10 mmHg diastolic

or

orthostatic systolic BP < 90 mmHg

within 3 minutes of orthostatic stress

Freeman et al., 2011; Brignole et al, 2018

When to think about orthostatic hypotension...

Symptoms of end-organ hypoperfusion:

Light-headedness, unclear thinking

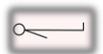
Blurred vision

Coat hanger or low-back pain

Angina, dyspnea

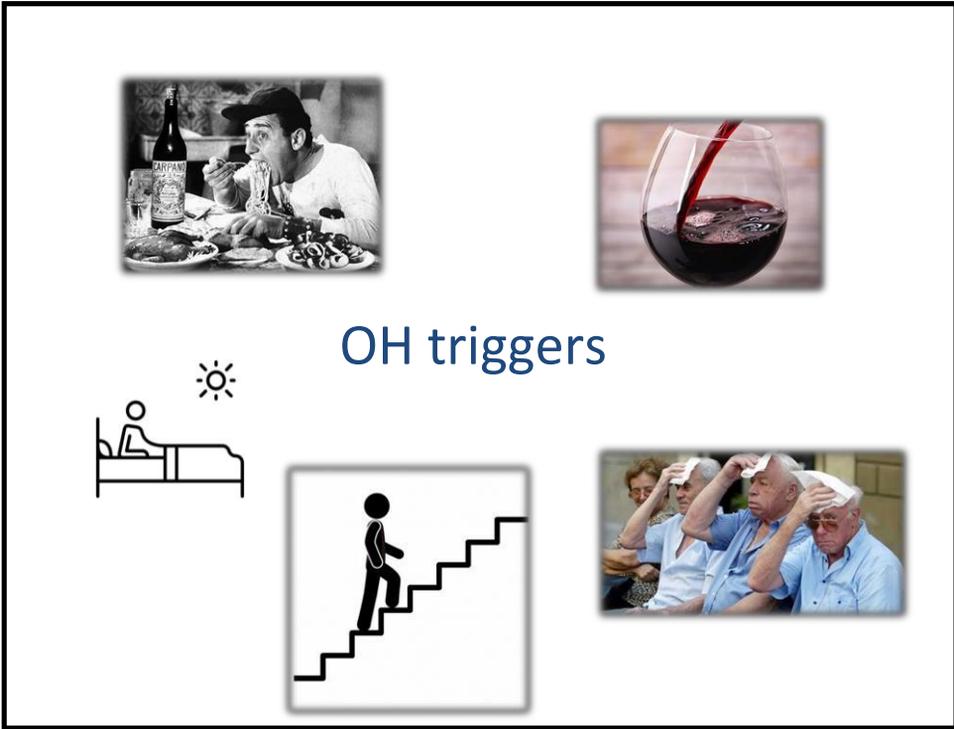


Symptoms develop upon standing



Symptoms ameliorate by lying down

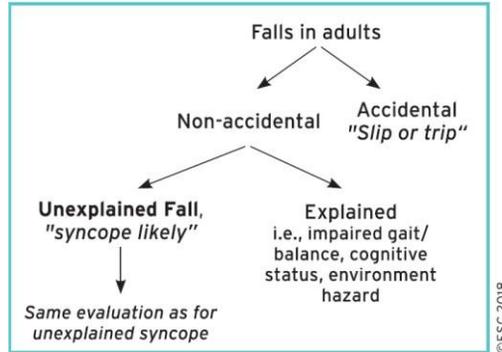
Orthostatic syncope



OH triggers

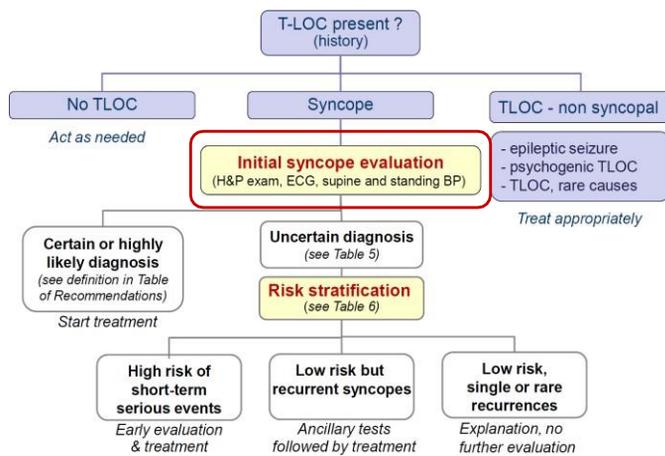


Unexplained fall > unexplained syncope



Brignole et al., 2018 ESC Syncope Guidelines

Initial evaluation



Brignole et al., Eur Heart J 2018

Linking history, signs and symptoms

Table 8 Association of orthostatic intolerance and orthostatic hypotension

		History of syncope and orthostatic complaints	
		Highly suggestive of OH; syncope and pre-syncope are present during standing, absent while lying, and less severe or absent while sitting; a predilection for the morning; sitting or lying down must help; complaints may get worse immediately after exercise, after meals or in high temperatures; no "autonomic activation"	Possibly due to OH; not all of the features highly suggestive of OH are present.
Supine and standing BP measurement	Symptomatic abnormal BP fall	Syncope is due to OH (Class I)	Syncope is likely due to OH (Class IIa)
	Asymptomatic abnormal BP fall	Syncope is likely due to OH (Class IIa)	Syncope may be due to OH (Class IIb)
	No abnormal BP drop	Unproven	Unproven

BP = blood pressure; OH = orthostatic hypotension.

© ESC 2018

Brignole et al., Eur Heart J 2018

What caused OH in Mrs Doubtfire?

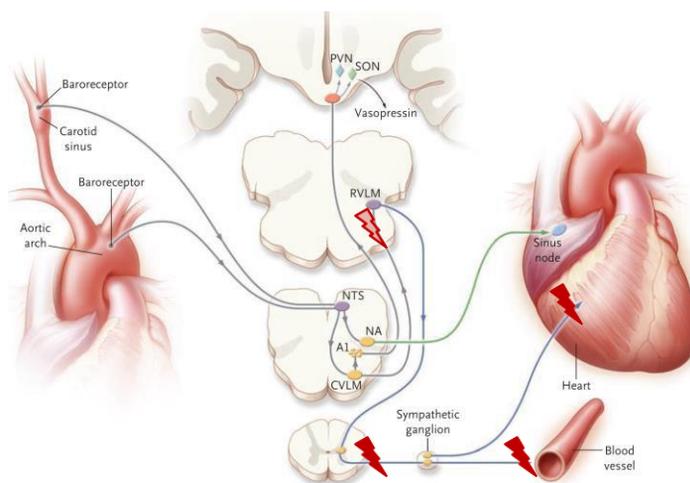
Most frequent causes

- Volume depletion:
 - Haemorrhage, diarrhea, vomiting, ecc
- Drug-induced:
 - vasodilators, diuretics, phenothiazine, antidepressants, dopaminergic drugs



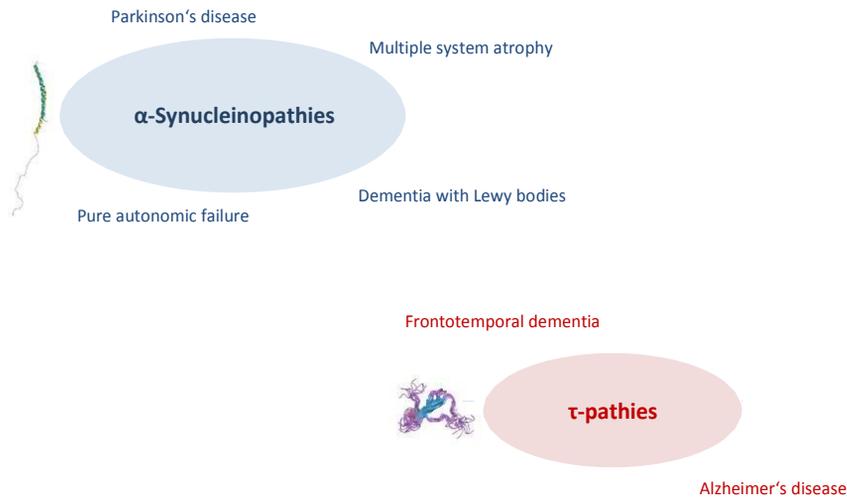
Only functional and reversible impairment of the autonomic nervous system

Neurogenic OH (nOH)



Adapted from Freeman, NEJM 2008

Primary neurogenic OH



Secondary neurogenic OH

- Metabolic causes (diabetes, ureamia)
- Amyloidosis (acquired, genetic)
- Spinal cord injury
- Infectious (HIV)
- Paraneoplastic (anti-Hu Ab, anti-CMRP-5 Ab)
- Immune-mediated (Guillain-Barré syndrome, acute autonomic ganglionopathy, Sjögren syndrome)

How to distinguish **OH** from **neurogenic OH**?

CLINICAL CONTEXT



Any hypotensive agent?
Any recent changes?



Cardiac arrhythmia?
Structural heart disease?



Anemia?
Any infection?



Any risk factor for nOH?

Mrs Doubtfire, 71-years old

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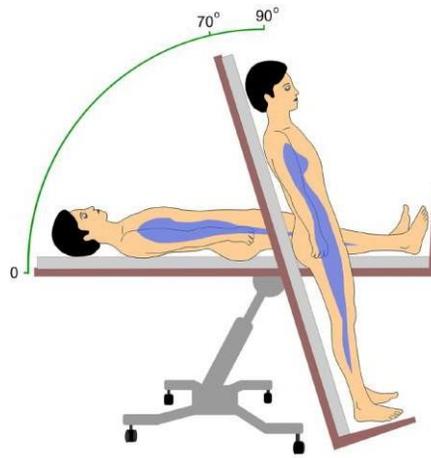
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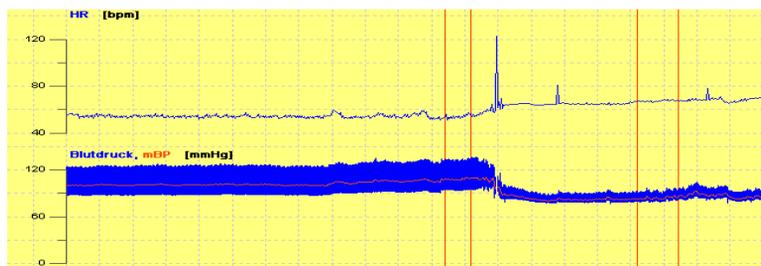
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Goldstein and Cheshire, CAR 2019

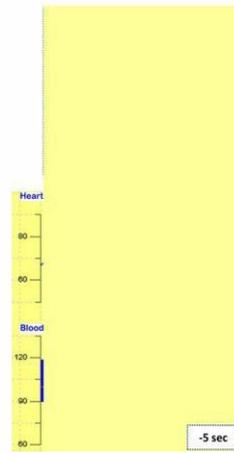
HR increase is blunted in nOH



$\frac{\Delta \text{ heart rate}}{\text{BP fall}} < 0.5 \text{ bpm/mmHg in nOH}$

Norcliffe-Kaufmann et al., Ann Neurol 2018

Valsalva manoeuvre test

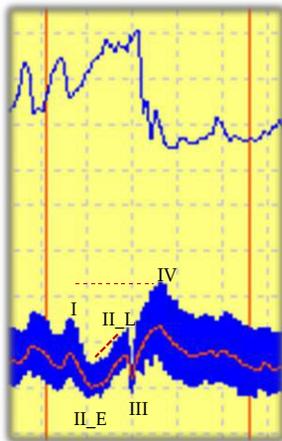


Recommendations	Class ^a	Level ^b
Valsalva manoeuvre Valsalva manoeuvre should be considered for assessment of autonomic function in patients with suspected neurogenic OH. ¹³⁸⁻¹⁴³	Ila	B

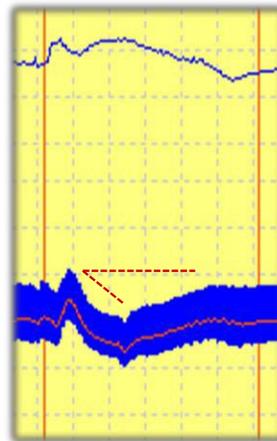
Brignole et al., Eur Heart J 2018

How to diagnose nOH?

Valsalva maneuver

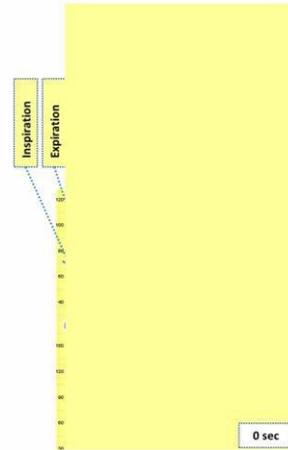


Healthy subject



Patient with nOH

Deep breathing test



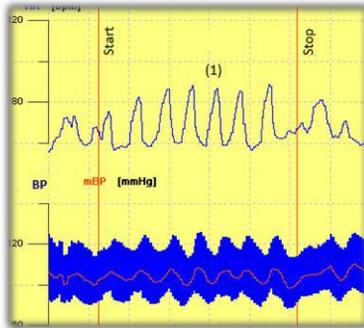
Deep breathing test
 Deep breathing test should be considered for assessment of autonomic function in patients with suspected neurogenic OH.^{142,143,146,147}

Ila	B
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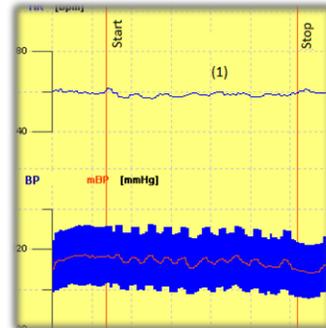
Brignole et al., Eur Heart J 2018

How to diagnose nOH?

Deep breathing



Healthy subject



Patient with nOH

Mrs Doubtfire has **neurogenic** orthostatic hypotension

What caused nOH in Mrs Doubtfire?

How to establish the **etiology** of nOH?

Age at onset

Childhood/teenage → Genetic disease

6th – 7th decade of life → Neurodegenerative diseases

Secondary nOH → age at onset depends on the underlying disease

How to establish the **etiology** of nOH?

Time course

- Episodic**
- Drug/ toxic exposure
 - Rare genetic disorders with autonomic crises
(HSAN III, acute intermittent porphyria)
- Acute/subacute** → Infectious, paraneoplastic, auto-immune
- Chronic/progressive** → Neurodegenerative diseases
- diabetic/uremic autonomic neuropathy

How to establish the **etiology** of nOH? *Neurological examination*

Isolated autonomic failure

- Anti-AchR Ab
- ¹²³I-MIBG cardiac SPECT
- Plasmatic NE

Autonomic failure + peripheral neuropathy

- Nerve conduction studies
- Laboratory tests:
 - blood cells count
 - fasting glucose, Hb1AC
 - Anti-SS-A, anti SS-B Ab
 - Onconeural antibodies
 - serum/urinary protein electrophoresis
 - HIV test

Autonomic failure + CNS involvement

- Neuroimaging
- DAT Scan
- Cognitive tests
- ¹²³I-MIBG cardiac SPECT
- Plasmatic NE

Mrs Doubtfire, 71-years old

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Mrs Doubtfire has **nOH**
due to diabetic autonomic neuropathy

Treatment

Management of symptomatic OH

Try to eliminate the cause whenever possible:

- Treat infections
- Treat anemia
- Reintegrate fluids
- Remove or reduce BP lowering drugs.

The NEW ENGLAND JOURNAL of MEDICINE

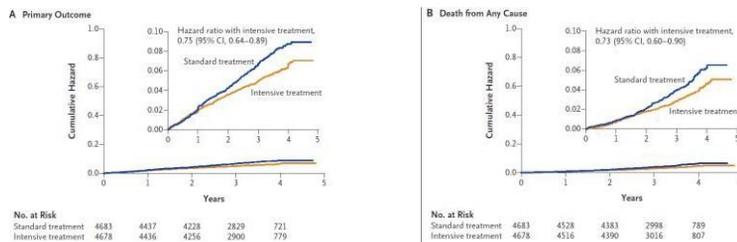
ESTABLISHED IN 1812

NOVEMBER 26, 2015

VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*



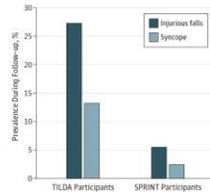
Intensive BP control lowers the risk of major cardiovascular events and death,
but increases the risk of hypotension, syncope, electrolyte abnormalities and acute
kidney failure.



In over 75 individuals...

The TILDA experience

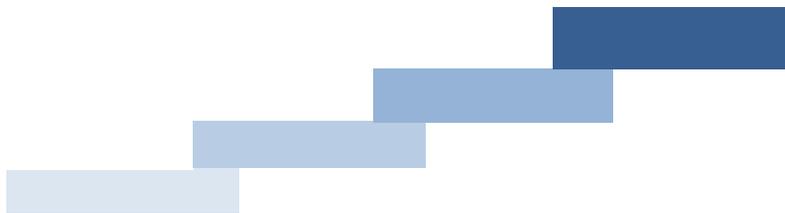
Figure. Comparison of the Prevalence Rates of Injurious Falls and Syncope Between the Systolic Blood Pressure Intervention Trial (SPRINT) and The Irish Longitudinal Study on Ageing (TILDA) Participants 75 Years or Older



Rate of syncope and injurious falls in individuals >75 years of age was 5-fold higher than in the SPRINT study. Intensive BP control may prove harmful in elderly patients.

Kenny et al., JAMA 2017

Management of neurogenic OH



Stepwise approach

Step 1

Review medication schedule

Step 2

Non-pharmacological measures



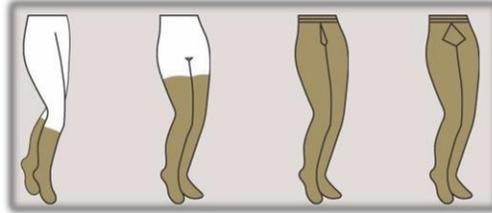
DON'Ts



DOs



Compression garments



Fanciulli et al., 2016

EBM treatment of nOH

Non-pharmacological measures

intervention	quality of evidence of reduction BP drop	recommendation	safety issues
1) non-pharmacological intervention			
abdominal binder	moderate	strong	none
sodium intake	low	weak	none
water	very low	weak	none
meal size	very low	weak	none
nocturnal head-up tilt position	very low	weak	none
physical counter maneuvers	very low	weak	none
compression stockings	very low	weak	none

Eschboeck et al., 2017

Step 3

Pharmacological measures

Pharmacological measures

- Plasma volume expansion
 - Fludrocortisone
 - DDAVP (Desmopressine)
- Sympathomimetics
 - Direct/indirect α_1 -adrenergic agents (Midodrine, Etilefrine)

Chobanian et al., 1979; Sakakibara et al. 2003; Jankovic et al., 1993; Low et al., 2000

Off-Label: Droxidopa



EBM treatment of nOH

Pharmacological measures

intervention	quality of evidence of reduction BP drop	recommendation	safety issues
2) pharmacological intervention for orthostatic hypotension			
midodrine	high	strong	supine hypertension, urinary retention, piloerection, scalp pruritus, paresthesia, chills, headache
droxidopa	moderate	strong	supine hypertension, headache, dizziness, fatigue, syncope, gastrointestinal complaints, urinary tract symptoms
atomoxetine	low	weak	not mentioned
octreotide	low	weak	effect on supine BP unclear
fludrocortisone	very low	weak	gastrointestinal side effects especially in gastroparesis, diabetogenic, hypernatremia, supine hypertension
pyridostigmine	very low	weak	supine hypertension, nausea, headache, lightheadedness, dizziness, edema, hypokalemia, renal and cardiac fibrosis (long-term), end organ damage (long-term)
yohimbine	very low	weak	gastrointestinal side effects, urinary urgency
fluoxetine	very low	weak	not mentioned, effect on supine BP unclear
ergotamine	very low	weak	gastrointestinal symptoms, symptoms referable to nervous system (e.g. headache, dizziness)
dihydroergotamine	very low	weak	nausea, vomiting, paresthesias, fatigue, fibrosis (retroperitoneal, cardiac, pleural, pulmonary), peripheral vasoconstriction, ergotism
erythropoietin	very low	weak	flu-like symptoms, allergic reactions, hypertension, increased risk of thrombosis
ephedrine	very low	weak	supine hypertension, dizziness, lightheadedness, photosensitivity, disequilibrium
phenylpropanolamine pseudoephedrine	very low	weak	supine hypertension, central sympathomimetic adverse events, cardiovascular events
indomethacin, ibuprofen, caffeine, methylphenidate and desmopressin	very low	weak	unclear

Eschlboeck et al., 2017

Step 4

Combined pharmacological measures

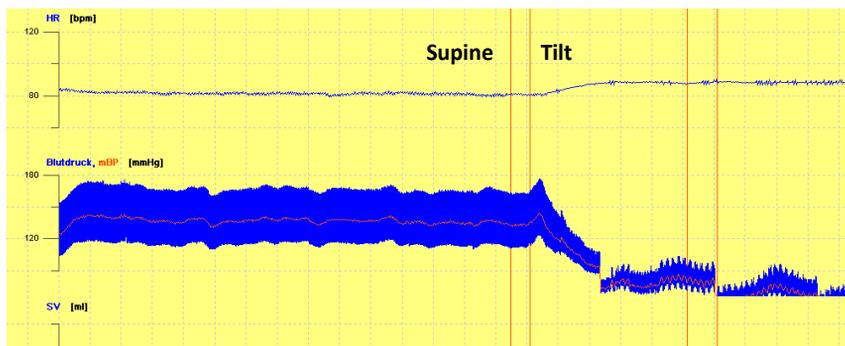


- Think about OH when a patient has symptoms upon standing, which ameliorate when supine.
- Use autonomic function tests to distinguish neurogenic OH from other causes of BP instability.
- If symptomatic, try to remove the cause of OH. Treat nOH with non-pharmacological and pharmacological measures in a stepwise approach.



Mr Smith, 62-years old

Which is your diagnosis?



Neurogenic orthostatic hypotension (nOH)
plus
neurogenic supine hypertension (nSH)



Consensus statement on the definition of neurogenic supine hypertension in cardiovascular autonomic failure by the American Autonomic Society (AAS) and the European Federation of Autonomic Societies (EFAS)

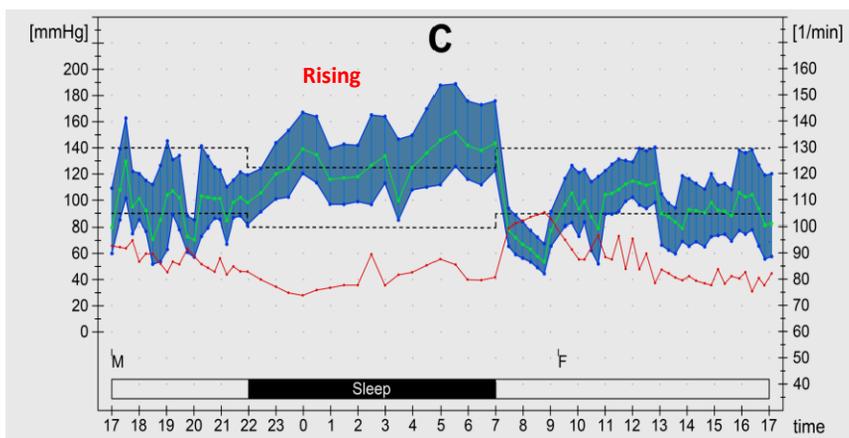
Endorsed by the European Academy of Neurology (EAN) and the European Society of Hypertension (ESH)

In patients with proven OH, SH is defined as **systolic BP ≥ 140 mmHg** and/or **diastolic BP ≥ 90 mmHg** measured after at least 5 minutes of rest in the supine position.

	Mild	Moderate	Severe
Systolic (mmHg)	140 – 159	160 – 179	≥ 180
Diastolic (mmHg)	90 – 99	100 – 110	≥ 110

Fanciulli, Jordan et al., CAR 2018

Nocturnal hypertension

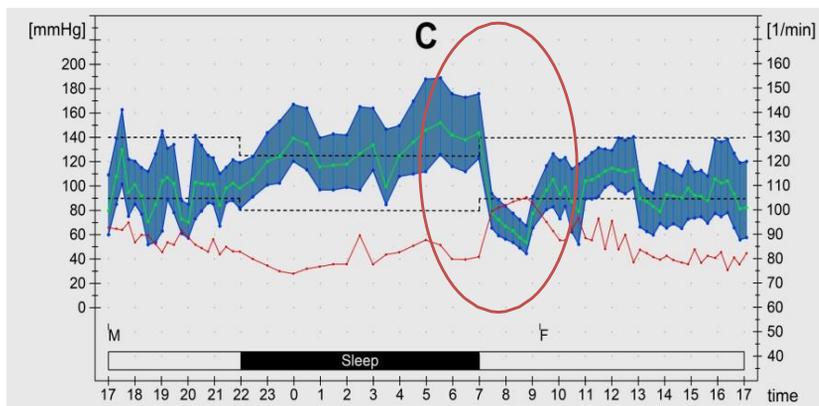


Fanciulli et al., 2014

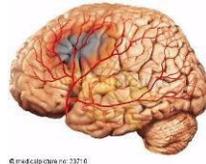
Would you treat hypertension in this patient?

Pressure natriuresis

Patients with supine hypertension loose up to 2 Kg weight overnight due to nocturia



Jordan et al., 1999; Fanciulli et al., 2014

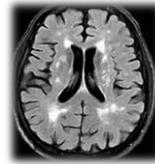
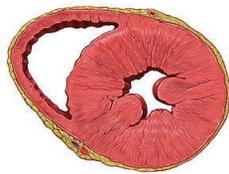


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Hypertensive emergencies



Frequency and influencing factors in patients with autonomic failure are still unknown

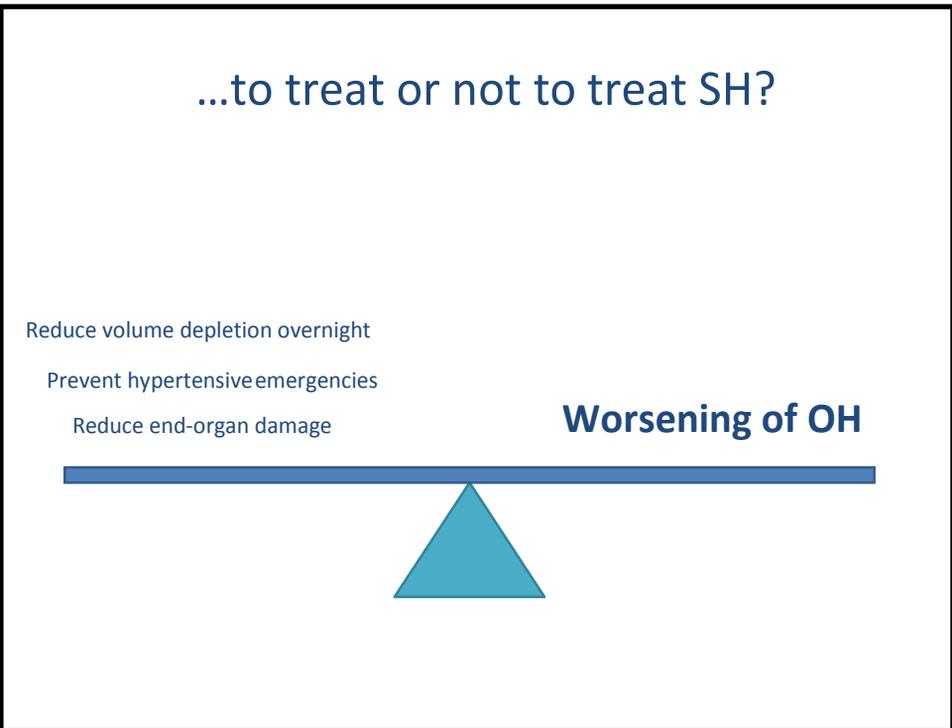
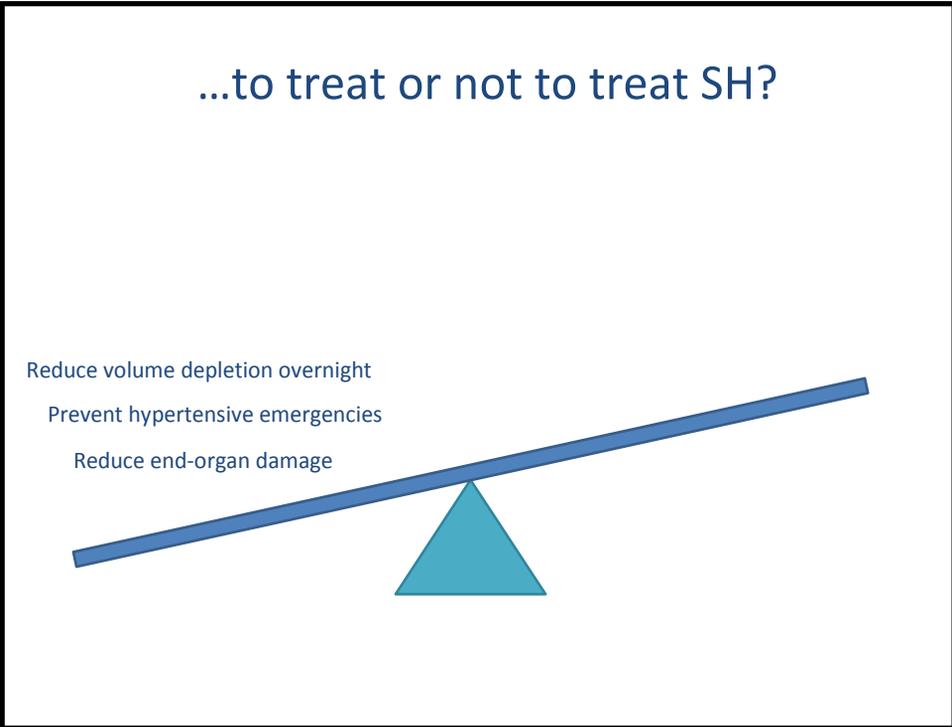


Increased end-organ damage

due to high **BP variability** (i.e. the combination of both very-low and very-high BP)



Rothwell, Lancet 2010



Screening for SH

Home BP monitoring

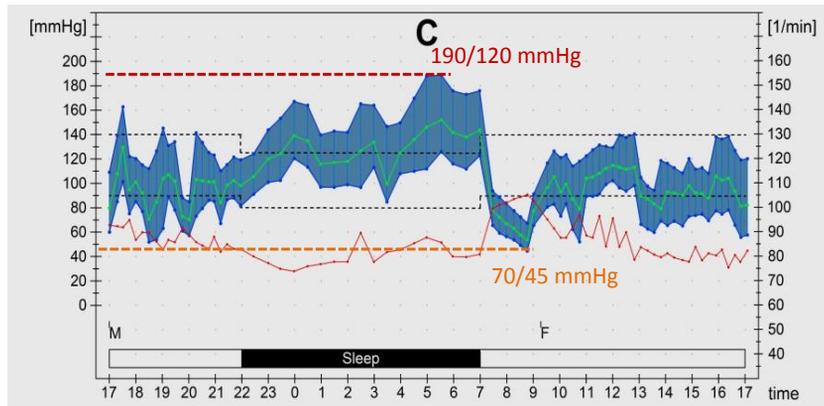


3 times/day early morning, midday, evening

3 positions supine, seated, standing

24h-ambulatory BP monitoring





Lowest and **highest** absolute BP values reached may be helpful to predict the risk of syncope and hypertensive emergencies in single patients.

Fanciulli et al., 2018

How to treat supine hypertension?



Consensus Document

Management of supine hypertension in patients with neurogenic orthostatic hypotension: scientific statement of the American Autonomic Society, European Federation of Autonomic Societies, and the European Society of Hypertension

Jens Jordan^{a,b,c}, Alessandra Fanciulli^d, Jens Tank^{a,b,c}, Giovanna Calandra-Buonaura^{e,f}, William P. Cheshire^g, Pietro Cortelli^{h,i}, Sabine Eschlboeck^d, Guido Grassi^{h,i}, Max J. Hilz^{h,k}, Horacio Kaufmann^l, Heinz Lahrmann^m, Giuseppe Manca^o, Gert Mayer^o, Lucy Norcliffe-Kaufmann^l, Anne Pavy-Le Traon^{p,q}, Satish R. Raj^{r,s}, David Robertson^t, Isabel Rocha^u, Hannes Reuter^{c,w,v}, Walter Struhal^w, Roland D. Thijs^{x,y}, Konstantinos P. Tsioufis^z, J. Gert van Dijk^z, Gregor K. Wenning^d, and Italo Bagnioni^f

Step 1

Preventive measures

How to prevent supine hypertension

- Avoid the supine position during daytime
 - Rest in a seated position
- Avoid offending agents (NSARs, SNRI)
- Limit water ingestion near bedtime
- Avoid long-acting pressor agents

Jordan et al., J Hypertension 2019

The half-life: to be kept in mind

Substance [active metabolite]	Half-life ^a (h)	Duration of effect ^b (h)
Short-acting drugs		
Midodrine [de-glymidodrine]	3 [3]	4-5
l-DOPS	1.5	4-5
Pyridostigmine	2	4
Yohimbine	0.5-1	>2
Indomethacin	2.5	4-6, >2
Ibuprofen	2	>2
Flurbiprofen	5-6	6
Phenylpropanolamine	2-3.5	>2
Dihydroergotamine	1.5-2	
Etilefrine	2.5	
Oxilofrine	4-6	
Metoclopramide	4	1-2
Domperidone	7-8	6
Atomoxetine	5	3-4
Long-acting drugs		
Fludrocortisone	3.5	1-2 days
Erythropoietin SC	4-12	
Others		
Octreotide SC	1.5	>3
Desmopressin	1.5-2.5	10-11

Kaufmann et al., 2013

Step 2

Non-pharmacological measures

Supine/nocturnal hypertension

Non-pharmacological measures

- Head-up tilt over night
- Small snack at bedtime
- If alcohol, small amount at bedtime



Step 3

Pharmacological measures

Supine/nocturnal hypertension

Pharmacological measures

Compound	Mechanism of action	Effect on nocturnal BP	Effect on nocturnal natriuresis	Effect on early morning OH	Side effects	Authors
Eplerenon 50 mg	Aldosteron antagonist	↓ systolic	Unchanged	Unchanged	Unknown	Arnold, 2016
Losartan 50 mg	ATII-R antagonist	↓ systolic ↓ diastolic	Reduced	Unchanged	Unknown	Arnold, 2013
Sildenafil 25 mg	PDE-5 inhibitor	↓ systolic	Unknown	Unknown	Unknown	Gamboa, 2008
Clonidin 0,1 mg	α2 – AR agonist	↓ systolic	Reduced	Unchanged	Unknown	Shibao, 2006
Nitroglycerin 0,1 mg/h (transdermal)	NO donor	↓ systolic	Unchanged	Unchanged	Unknown	Shibao, 2006
Nifedipin	Ca2+ Blocker	↓ systolic	Increased	Increased	Unknown	Jordan 1999



- About 50% of patients with neurogenic OH suffer from supine and nocturnal hypertension, with short-term and long-term morbidity and mortality risk.
- Plan treatment on the basis of home and 24h BP monitoring
- Management relies on preventive, non-pharmacological and pharmacological measures.



Male, 72-years old

Experiences a near-syncope at the post office on a warm day: he started feeling dizzy, breathless, could not read the numbers on the screen anymore, but still managed to sit down, with symptomatic relief. Back at home takes the blood sugar: 127 mg/dL.

Medical history: diabetes mellitus, hypertension.

Medication: metformin, metoprolol

On status: unremarkable, normal cognition.

Physical examination: slight dehydrated skin, otherwise normal.

ECG: sinus Rhythm, 67 bpm, PQ = 150 msec, QTc = 390 msec, normal repolarization.

Male, 72-years old

Supine BP: 133/91 mmHg

1' minute standing BP: 135/89 mmHg

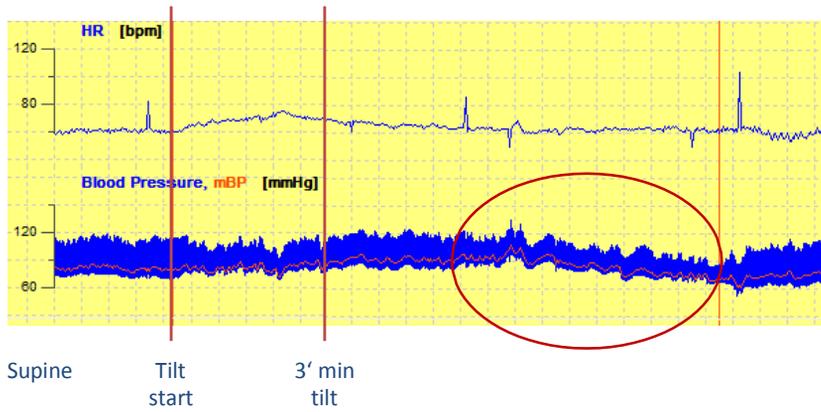
3' minute standing BP: 124/87 mmHg

5' minute standing BP: 118/85 mmHg

-15/-6 mmHg, no symptoms

Would you refer this patient for a head-up tilt test?

Male, 72-years old



Delayed orthostatic hypotension (dOH)

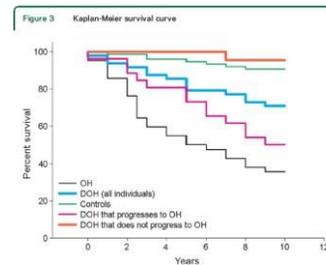
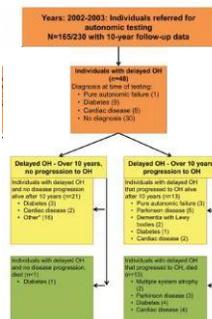
BP fall ≥ 20 mmHg systolic or ≥ 10 mmHg diastolic
occurring beyond 3 minutes of orthostatic stress

Brignole et al, 2018



Clinical implications of delayed orthostatic hypotension

A 10-year follow-up study



44% of patients with dOH develop overt OH over 10 years and 1/3 an α -synucleinopathy.

Mortality rate is 50% in these patients.

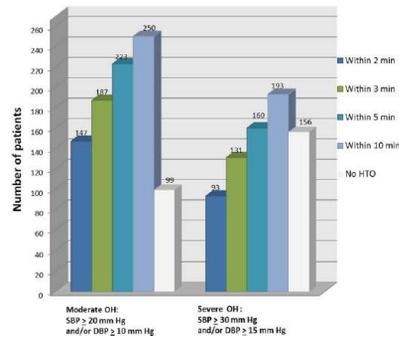
Autonomic

RESEARCH PAPER



New insights into orthostatic hypotension in multiple system atrophy: a European multicentre cohort study

A Pavy-Le Traon,^{1,2} A Piedvache,³ S Perez-Lloret,^{4,5} G Calandra-Buonaura,^{6,7} V Cochen-De Cock,^{1,8} C Colosimo,⁹ P Cortelli,^{6,7} R Debs,¹ S Duer,¹⁰ A Fanciulli,¹⁰ A Foubert-Samier,^{11,12,13} A Gerdelat,¹ T Gurevich,¹⁴ F Krüger,¹⁰ W Poewe,¹⁵ F Tison,^{11,12,13} C Tranchant,¹⁶ G Wenning,^{10,15} O Rascol,^{1,4} WG Meissner,^{11,12,13} on behalf of the European MSA Study Group



Prolonged orthostatic challenge raises the sensitivity for OH in MSA



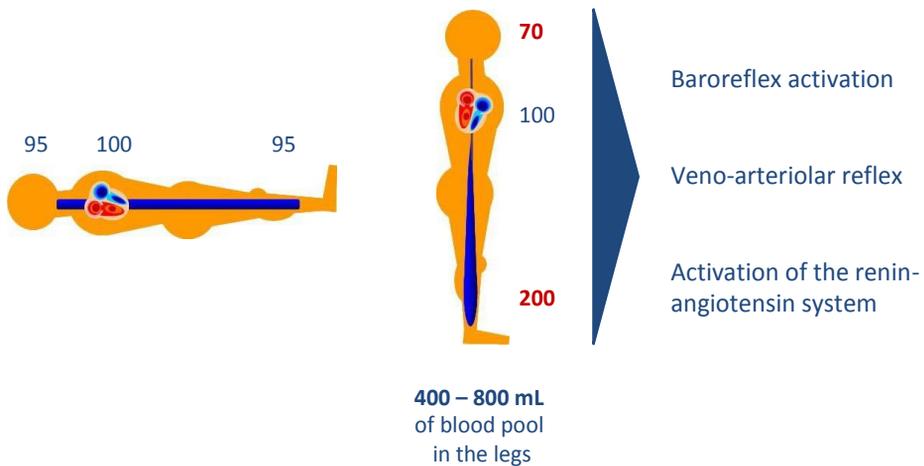
- OH sometimes develops after the standard 3 minutes of orthostatic challenge.
- Prolonged standing or head-up tilt may help identifying delayed OH.
- Delayed OH may indicate an incipient α -synucleinopathy and an increased mortality risk.



It's a matter of few seconds...

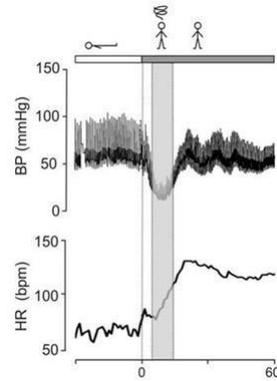
Cardiovascular adaptation upon standing

Mean arterial pressure (mmHg)



Courtesy of Prof. Anne Pavy Le Traon

Initial OH



Transient BP fall ≥ 40 mmHg systolic or ≥ 20 mmHg diastolic within 15 seconds after standing-up

Moya et al., 2009



Initial OH is frequent in the elderly population (**20-40%**) and associated with falls, orthostatic intolerance and frailty.

Finucane C et al., 2014 Romero-Ortuno R et al., 2011

What about Parkinson's disease?

Transient orthostatic BP changes in PD

Retrospective study in 167 patients with PD (31 with PD dementia)

HR and BP values sampled at:

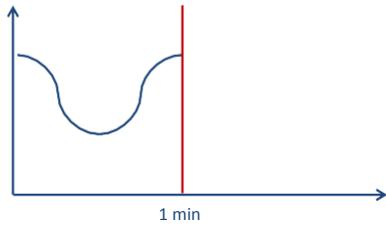


Fanciulli, Campese et al., *in preparation*

Methods

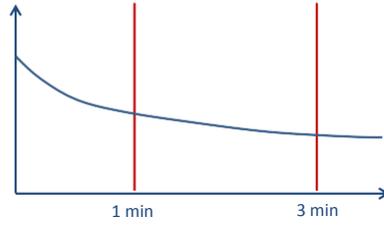
TRANSIENT BP FALLS

Transient decline $\geq 20/10$ mmHg limited to the 1st minute upon standing

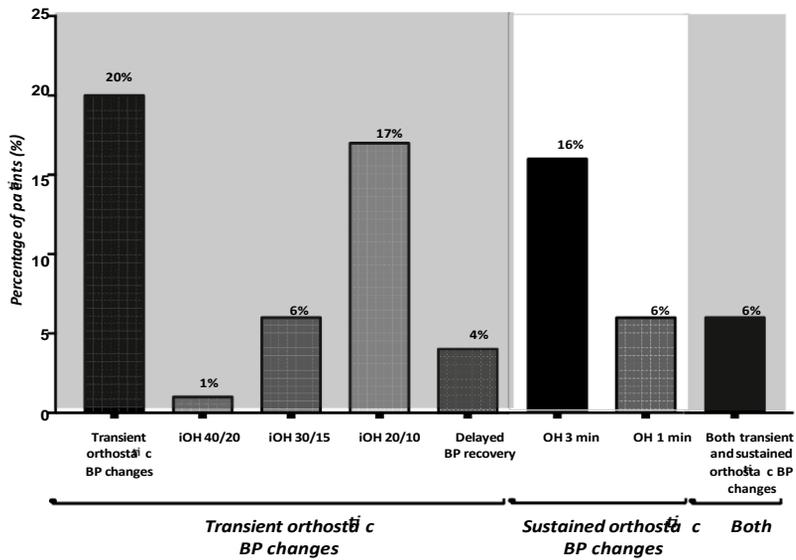


SUSTAINED BP FALLS

Sustained decline $\geq 20/10$ mmHg 1 minute or 3 minutes after standing



Fanciulli, Campese et al., in preparation



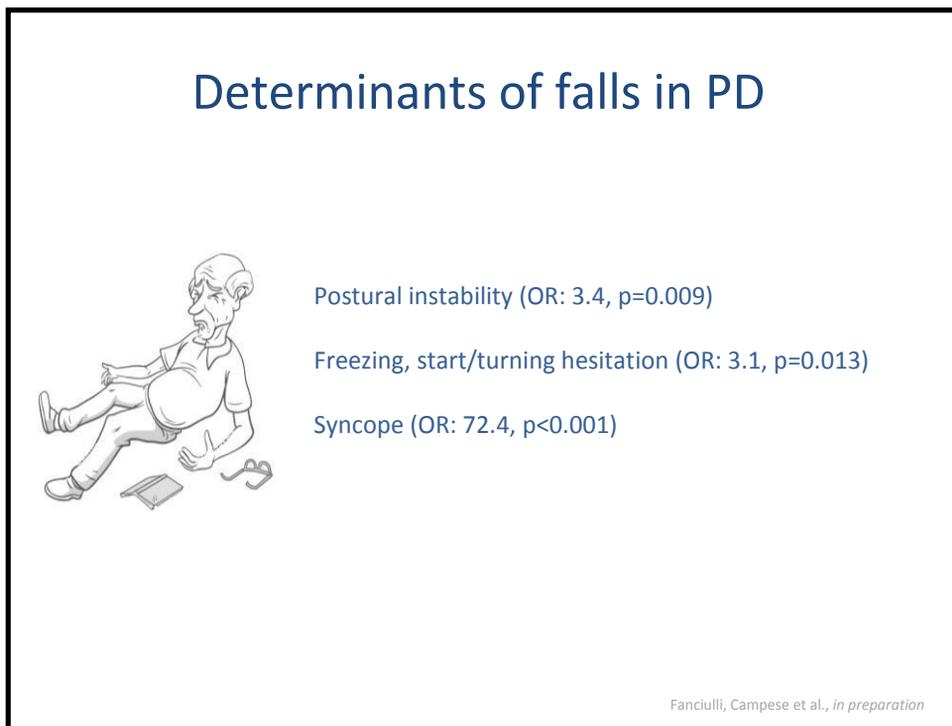
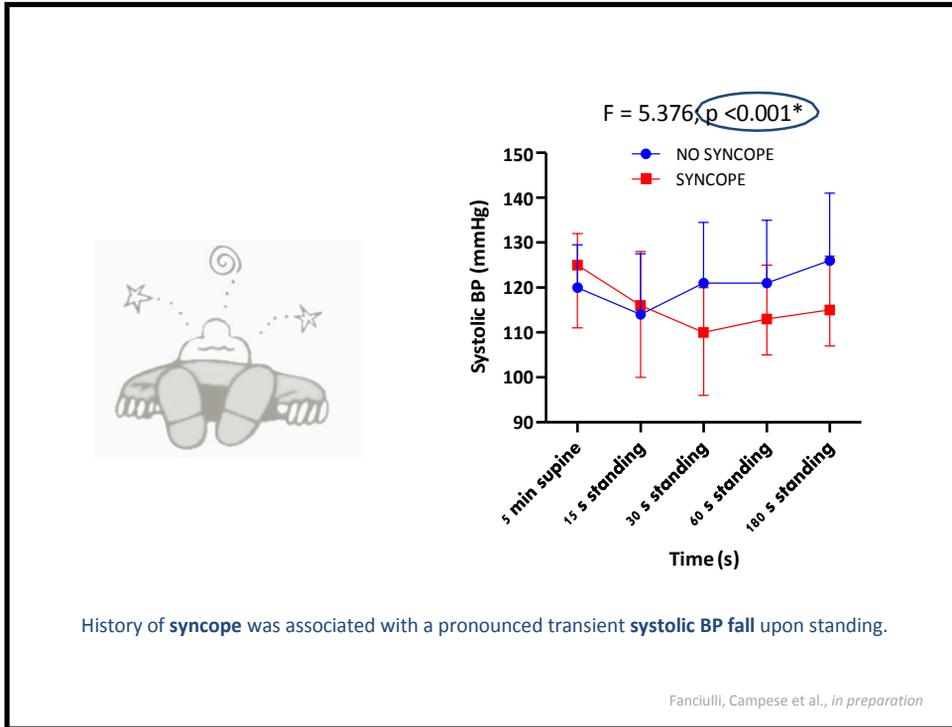
Fanciulli, Campese et al., in preparation



No difference in the frequency of falls, syncope or orthostatic
intolerance among the orthostatic BP categories

Fanciulli, Campese et al., *in preparation*

BUT....





- Transient orthostatic BP changes affect about 20- 40% of the population.
- Greater systolic BP falls within 30 s upon standing are associated with syncope and orthostatic intolerance in elderly individuals and patients with PD.
- Continuous HR and BP monitoring upon standing may help identify a treatable cause of syncope and falls in these patients.

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