How to manage a patient with autonomic dysfunction - Level 2

How to manage autonomic failure with sleep disorders

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Nocturnal autonomic symptoms in primary autonomic failure
Diagnosis and management

Prof. Pietro Cortelli

Primary autonomic failure
- Pure Autonomic Failure (PAF)
- Multiple system atrophy (MSA)
- Lewy Body Dementia (LBD)
- Parkinson's disease with dysautonomia

Nocturnal autonomic symptoms
- supine hypertension
- sleep-related breathing disorders
- nocturia
- thermoregulation dysfunction

Sleep, regulated by brainstem and diencephalic structures interconnected with the autonomic nervous system (ANS), and is associated with changes in ANS activity.

Several neurological disorders are associated with dysfunction of the autonomic cardiovascular and respiratory control during sleep, with negative impact on prognosis.

Conflict of interest: The author has no conflict of interest in relation to this manuscript
Blood pressure fluctuates with a pattern that follows a circadian rhythm:
- peak in the early morning hours
- trough during sleep

Circadian rhythms originate from the suprachiasmatic nuclei of the anterior hypothalamus but the autonomic nervous system is suspected to play a role.

Orthostatic hypotension is the most frequent clinical feature of cardiovascular autonomic failure in parkinsonian syndromes (50% in PD and 75% in MSA).

In half of the cases, OH can be accompanied by supine hypertension (SH), in particular during night rest (nocturnal hypertension) → syndrome “Orthostatic Hypotension-Supine Hypertension”

Supine hypertension in nOH patients is arbitrarily defined as:
- a systolic blood pressure ≥ 150 mmHg
- a diastolic blood pressure ≥ 90 mmHg

The diagnostic gold standard for detecting nocturnal hypertension is 24-h ambulatory blood pressure (BP) monitoring (24-h ABPM).

Pathological nocturnal BP profiles:
- non dipping profile: nocturnal BP reduction lower than 10% with respect to daytime values
- reverse dipping: BP increases during night time
- pathological nocturnal blood pressure profile, either non-dipping or reverse dipping, occurs in more than 50% of subjects diagnosed with MSA or PD

- the co-occurrence of OH and nocturnal hypertension has been recently suggested to play a negative prognostic role on survival, cognitive, cardio- and cerebrovascular outcome in parkinsonian syndromes

- specific cut-off values to diagnose nocturnal hypertension in patients with cardiovascular autonomic failure are missing at present

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Management approaches to hypertension in autonomic failure

Amy C. Arnold and Paolo Biaggioni

Non pharmacological measures

1. avoid medications that increase blood pressure such as nasal decongestants, eye drops containing sympathomimetics and NSAIDs

   ✓ there is no agreement among clinicians, when, or how vigorously supine hypertension should be treated with nOH

   ✓ there is no clinical study evidence to base guidelines

   ✓ the decision to treat should be individualized

2. elevation of the bed's head (20-30 cm) during the night, reducing nighttime pressure natriuresis and improving morning orthostatic tolerance in autonomic failure
Pharmacological measures

- transdermal nitroglycerin patches (0.025-0.2 mg/h) applied at bedtime and removed in the morning does not improve orthostatic intolerance in the morning

- oral administration of other vasodilators including hydralazine (50 mg to 100 mg) and minoxidil (2.5 mg) less potent

- short-acting calcium channel blocker nifedipine (30 mg) induces natriuresis and may lower standing morning blood pressure

- sildenafil (25 mg)

- in MSA patients, in whom supine hypertension can be driven by residual sympathetic tone, can be useful the central sympatholytic clonidine (0.1 mg) but does not improve morning orthostatic tolerance for residual effects of the medication

Raccomandations

- ideal pharmacologic agent
  - lower blood pressure during the night
  - not worsen orthostatic hypotension in the morning

- pharmacological treatment of supine hypertension could potentially aggravate orthostatic hypotension during the night, increasing the risk of falls in patients

- treatment of supine hypertension, therefore, should only be directed to patients who would benefit the most
Sleep-related respiratory dysrhythmias

- Obstructive sleep apnea → MSA and PD
- Central sleep apnea → MSA
- Cheyne-Stokes breathing, dysrhythmic breathing, apneustic breathing, inspiratory gasping, inspiratory stridor → MSA


Similar articles

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Sleep Dysfunction in Multiple System Atrophy
Luigi Ferini-Strambi, MD, PhD
Sara Morelli, PhD

Obstructive apnea

- occurs more frequently than central sleep apnea (15-37%)
- narrowing of the upper airway at the level of the vocal cords, hypokinesia, rigidity, dystonia and paralysis of the upper airway muscles may predispose
- in early stages of the disease CPAP is effective long-term therapy is an effective treatment
- floppy epiglottis is a contraindication of CPAP for possibility that downward displacement of the epiglottis and upper airway obstruction
Central apnea

- is commonly found in later stages of MSA but may be the presenting feature in a few cases.

- in patients with obstructive sleep apnea, after the elimination of obstructive events by CPAP, it is possible to observe central apneas.

- **CPAP with adaptive servoventilation algorithm** may be used → this device is designed to rapidly normalize SRBD with both central and obstructive components.

"Sleep Dysfunction in Multiple System Atrophy" - L.Ferini-Strambi et al., 2012

Causal hypotheses

1. dystonia in adductor muscles (thyroarytenoid muscles) → supported by the observation that botulinum toxin can ameliorate laryngeal stridor

2. abductor muscle weakness (cricoarytenoid muscles) → nucleus ambiguus lesion results in hypoactivity of a laryngeal abductor

3. depletion of serotonergic neurons in the medullary raphe nuclei → recently identified in cases of MSA
Sleep disorders in multiple system atrophy: a correlative video-polysomnographic study

Roberto Vetrugno\textsuperscript{a,b}, Federica Provenzi\textsuperscript{a}, Pietro Cortellì\textsuperscript{b}, Giuseppe Plazzi\textsuperscript{a}, Enrico M. Lotti\textsuperscript{a}, Giulia Pierangeli\textsuperscript{b}, Carlotta Canali\textsuperscript{b}, Pasquale Montagna\textsuperscript{b}

- **Inspiratory noise** was universal
- **Expiratory noise** was found in nearly 4/5 of patients
- **Stridor** was found in nearly half of patients
- **OSAS** in 37% of patients

- mild (93.3%) O2 desaturation occurred during sleep even unassociated with OSAS or stridor, indicating that sleep-related O2 desaturation may be intrinsic to the disease

<table>
<thead>
<tr>
<th>patients with stridor, already tachypnoic du from wake to NREM and REM sleep</th>
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<td>their HR did not significantly decrease in NREM sleep</td>
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<tr>
<th>Table 1: Mean breathing and heart rate during wake, NREM, and REM sleep</th>
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<td><strong>Wake</strong></td>
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<td>(mean ± SD)</td>
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<td>Mean breathing rate</td>
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<td>MIA patients (n=19)</td>
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Early diagnosis and stage classification of vocal cord abductor paralysis in patients with multiple system atrophy

Eiji Isumaki, Akiro Nari, Sanoshi Horiguchi, Rie Kawamura, Tensuro Hayashida, Riishi Tanabe

- analysis of vocal cord movement by laryngoscopy during wakefulness and also during sleep induced by diazepam (5-10 mg)

- the vocal cords in patients with MSA and VCAP showed dramatic paradoxical movement only during sleep, although their movement when awake was normal

Division of VCAP (vocal cord abductor paralysis) into four stages according to the laryngoscopic findings

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<th>Table 3: Stage classification of vocal cord abductor paralysis on laryngoscopy</th>
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<td>Vocal cord movement</td>
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<td>Stage</td>
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<td>Stage 1 (normal)</td>
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<td>Stage 2 (mild)</td>
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<td>Stage 2 (moderate)</td>
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<td>Stage 3 (severe)</td>
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Paradoxical vocal cord motion: A review focused on multiple system atrophy

Keisuke Shiba a,b,*, Shiroh Isono c, Ken Nakazawa d

- in the **early stage**, restricted dilatation of the vocal cords in some patients with laryngeal dysphagia can reveal slight restricted abduction.
- in the **middle stage**, restricted dilatation is readily observed.
- in the **advanced stage**, adductor paralysis as well as daytime stridor often appears.

*Laryngoscopic examination* during diazepam or propofol-induced sleep can reveal glottal narrowing during inspiration, and thus confirms the diagnosis of laryngeal stridor.

This paradoxical inspiratory activation of the adductor is abolished by application of continuous positive airway pressure (CPAP) and by tracheostomy.

![Diagram showing the effects of CPAP and tracheostomy on laryngeal function](image-url)

**Fig. 2.** Effects of continuous positive airway pressure (CPAP) (A) and tracheostomy (B) on paradoxical inspiratory activation of the vocal cords and adductor in MSA patients. (A) Note the disappearance of adductor inspiratory activation during CPAP application, indicated by the thick horizontal line through the larynx. The **adductor** was activated during the inspiratory phase with inspiration flow limitation but absent upper airway breathing. The adductor inspiratory activation was abolished after breathing was diverted to the tracheostomy (right panel); [stimulating the larynx](image-url).
Therapeutic aspect

1. Continuous positive airway pressure (CPAP)
   - non-invasive therapy, used in the initial management (treatment of first line)
   - the severity of motor impairment is the most significant limiting factor for long-term acceptance
   - used with caution in patients with dysphagia because of the theoretical potential for aspiration pneumonia
   - floppy epiglottis is a contraindication for the use of CPAP → in this regard titration with fiberoptic laryngoscopy is recommended

"Laryngeal stridor in multiple system atrophy: Clinicopathological features and causal hypothesis" T.Ozawa et al.; 2016

2. Tracheostomy
   - in case of severe airway obstruction and if CPAP is not tolerable should be considered
   - is first indicated when stridor is present during wakefulness because of the high risk of respiratory failure and death
   - it is possible aggravation of central sleep apnea after tracheostomy → in this regard, the severity of central sleep apnea should be evaluated using overnight polysomnography if tracheostomy is being considered
   - tracheostomy may deprive the patient of phonatory function → quality of life in MSA patients should also be considered

"Laryngeal stridor in multiple system atrophy: Clinicopathological features and causal hypothesis" T.Ozawa et al.; 2016
3. Other treatments are:
   - **botulinum toxin** → possibility of vocal cord paralysis
   - laryngeal surgery such as **unilateral cordectomy** or **laser arytenoidectomy**

   *These two therapies are limited and they may increase the risk of bronchial aspiration*

Since the depletion of medullary serotonergic neurons discovered in patients with MSA, **serotonergic neurotransmission** may represent a therapeutic target for laryngeal stridor in this population:

- Ozawa et al. tried serotonergic therapy using a **selective serotonin reuptake inhibitor** in three patients with MSA, revealing that two of the three patients showed obvious improvements in glottic stenosis after SSRI therapy, and the remaining patient achieved improvement in the threshold of airway pressure required to maintain glottic opening.

   **CPAP and tracheostomy increase survival in MSA!**

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**CLINICAL REVIEW**

Sleep disordered breathing in Parkinson's disease: A critical appraisal
Francisco P. da Silva-Júnior a, b, Gilmar F. do Prado b, Égberto R. Barbosa b, Sergio Tufla b, Silvia M. Tognetto b

- included cross-sectional and longitudinal studies to define the prevalence of SDB in idiopathic PD → 7 publications included

1. a **five studies** showed that PD patients have a **similar or even smaller** amount of obstructive apneas and hypopneas during sleep than controls

2. b **two studies** (Maria et al. and Shpirer et al.) reported a greater median AHI for PD patients when compared to controls

3. **four studies** investigated central sleep apnea and none of them found a higher index for PD patients
“Are sleep related breathing disorders more prevalent in PD than in the general population?”

- Several factors can predispose patients with PD to develop OSA:
  - PD patients are usually elderly
  - PD patients have abnormalities in the upper airway (hypokinesia and rigidity) and in pulmonary function
- In contrast, PD may be protected from OSA for lower weights than age-matched healthy controls
- Lack of association between AHI and PD duration and severity → SDB in PD does not seem to be a disease-related process

“Sleep disordered breathing in Parkinson’s disease: A critical appraisal”
J.P.de Silva-Junior et al., 2014

Nocturnal Body Core Temperature Falls in Parkinson’s Disease but Not in Multiple-System Atrophy

G. Pizzagalli, MD, PhD, 1, 1 F. Previti, MD, 1, 1 P. Maltoni, MD, 1, 1 G. Budariz, 1 M. Cotrin, MD, 1, 1 E. Lugaresi, MD, 1, 1 P. Monnuga, MD, 1, 1 and P. Costell, MD, PhD

**Aim was to assess the CRT* as an index of central autonomic function in IPD and MSA to distinguish the two diseases**

- 48 hours-monitoring rectal temperature every 2 min in IPD, CN and MSA
- IPD and CN showed similar physiological nocturnal fall of BCT*
- significantly higher BCT* during nonREM and REM sleep in MSA compared to CN and IPD

The impaired CRT* in MSA is probably due to an inability to reduce sympathetic activity during sleep i.e. to the inability to produce the peripheral vasodilatation necessary for the physiological nocturnal heat loss and consequent BCT* fall
REM behaviour disorder

RBD diagnosis

According to the third edition of the International Classification of Sleep Disorders (2012), the following criteria are required to make a diagnosis of RBD:
1. Repeated episodes of sleep-related vocalization and/or complex motor behaviors;
2. These behaviors are documented by PSG to occur during REM sleep, or based on clinical history of dream enactment, and are presumed to occur during REM sleep;
3. Polysomnographic recordings demonstrating RSWA; and
4. The disturbance not better explained as another sleep disorder, mental disorder, medication, or substance use.

- parasomnia with history of recurrent nocturnal dream enactment behavior and loss of skeletal muscle atonia and increased phasic muscle activity during REM sleep: REM sleep without atonia (RSWA)

- very strong associations have been identified between RBD and the alpha synucleinopathies

Treatment of REM Sleep Behavior Disorder

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In spring International Business, New York, 1998

- Clonazepam → recommended dose is 0.25–2.0 mg taken 30 min before bedtime

- Melatonin, given in high doses, has been shown to be as efficacious as clonazepam in controlling RBD symptoms and appears to have improved tolerability and a better adverse effect profile than clonazepam

- Ramelteon, a melatonin receptor agonist, given at doses of 8 mg/day

- Agomelatine is an antidepressant that in part acts as a melatoninergic agonist (25 mg taken 1 h prior to bedtime)
- **dopamine agonists** such as pramipexole has produced mixed results → it can be considered as a *third-line medication option* or in patients with co-morbid restless legs syndrome.

- The effects of **acetylcholinesterase inhibitors** are not clear → *third line treatment* with a similar role as dopamine agonists for patients who have failed clonazepam or melatonin, or used in symptomatic RBD patients requiring concurrent treatment for cognitive impairment.

- **Sodium oxybate** (4,5 to 6 g) was shown to improve RBD symptoms in patients not responsive to other conventional treatment options.