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European Reference Network for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

8th ERN EURO-NMD Annual Meeting

Sleep in Neuromuscular Disorders

5th – 7th March 2025

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The ERN EURO-NMD is funded by the European Commission under the EU4Health programme (EURO-NMD 23-27 — 101156434 — EU4H-2023-ERN2-IBA)

DOI

Speaker honoraria: Amicus, Sanofi, Biogen, ITF

Advisory boards: Amicus, Sanofi

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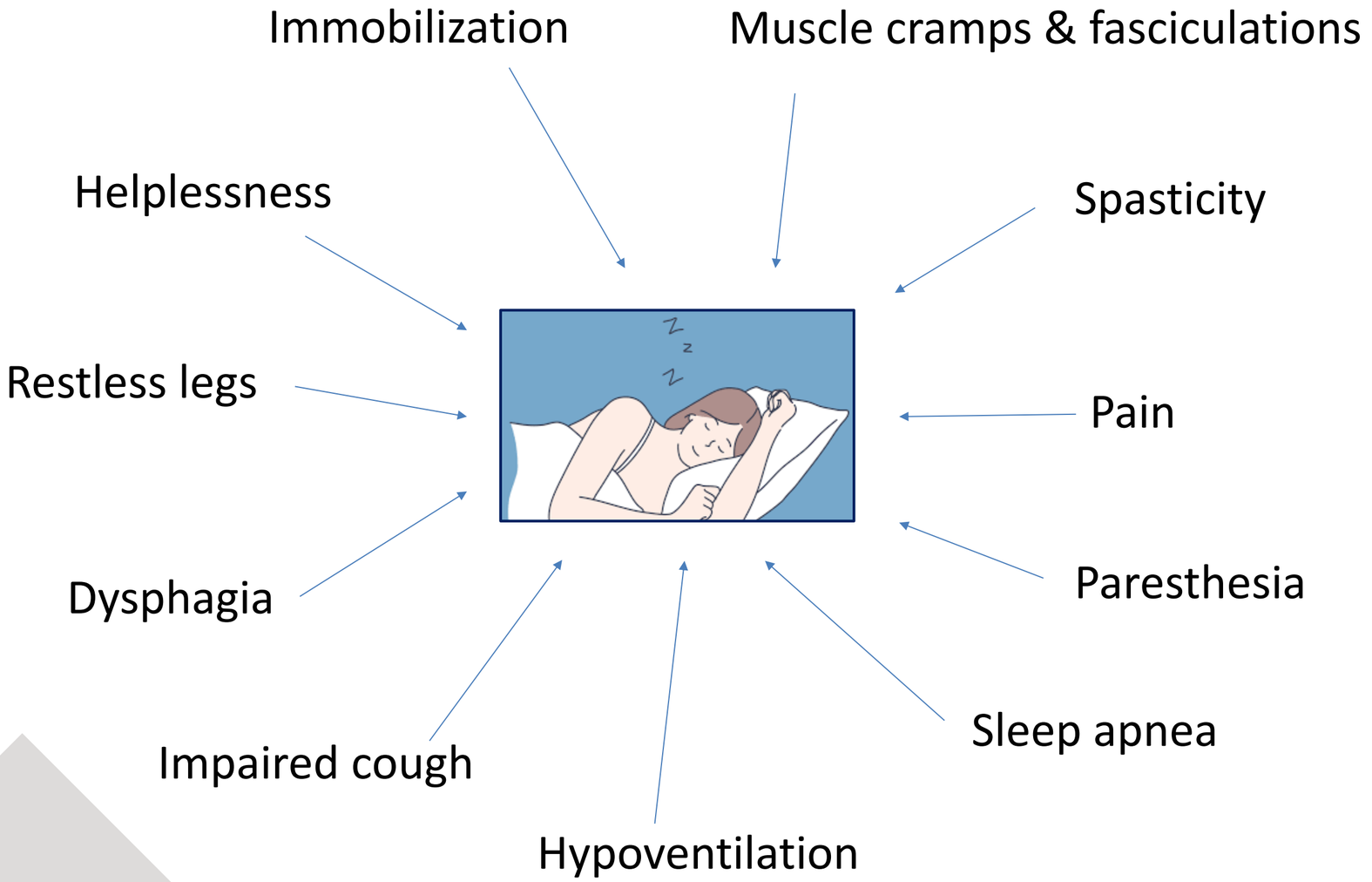
Troublemakers: Sleep disruptors in NMD



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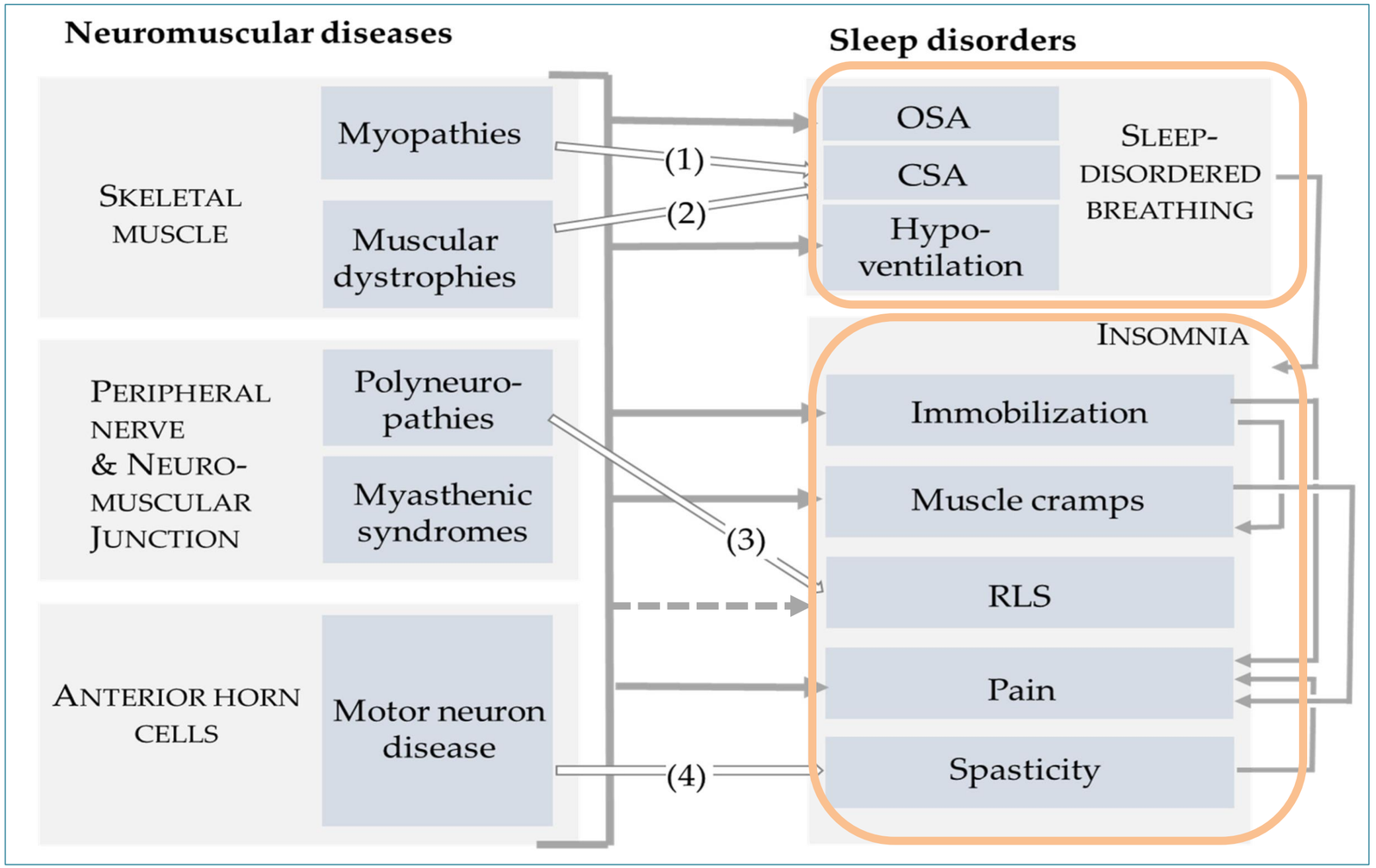
Sleep disturbances in NMD



(1) Mitochondriopathies
(2) Myotonic dystrophies
(3) Sensory and sensorimotor neuropathies
(4) Amyotrophic lateral sclerosis, primary lateral sclerosis, and hereditary spastic paraplegia.

Boentert, M et al. Clin. Transl. Neurosci. 2023.

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Muscle cramps

- Common in the general population
- Very frequent in NMD
- Lower motor neuron sign
- Legs > arms
- Neurogenic > myogenic
- Worsened by diabetes, electrolyte imbalances, dehydration, alcohol, thyroid disease
- Worsened by diuretics, sympathomimetics, statins

Treatment:

- Avoid triggers & causes
- Try stretching of affected muscle groups
- Try oral Mg or Ca
- Try quinine, but carefully
- Few trials only, e. g. mexiletine in ALS

NB: Cramps are different from spasticity!

1. American Academy of Sleep Medicine. International Classification of Sleep Disorders 3rd ed (ICSD-3) 2014.
2. Naylor JR, Young JB. Age Ageing. 1994 Sep;23(5):418–20.
3. Daniell HW et al. JAMA Intern Med. 2013 May 27;173(10):934–5.
4. Blyton F et al. Cochrane Database Syst Rev. 2012 Jan 18;1:CD008496.
5. Weiss MD et al. Neurology. 2016;86:1474–81.

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Spasticity

- Upper motor neuron sign
- Legs > arms (mostly)
- Triggered by movements & spontaneous

Treatment:

- Systemic: baclofen, tizanidine, diazepam, tolperisone, cannabinoids
- Focal: botulinum toxin

1. Kerstens, H.C.J.W. et al. Orphanet J. Rare Dis. 2021
2. Chou, R. et al. J. Pain Symptom Manag. 2004
3. Lapeyre, E. et al. NeuroRehabilitation 2010

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Pain

- Extremely common & important
- Majority of patients with FSHD, inflammatory myopathies, ALS
- Never underestimate
- Nociceptive, neuropathic or by central sensitization
- Spontaneous or related to immobilization

Treatment:

- Provide alleviation where and as needed (bed comfort, positioning, medical aids)
- Pharmacotherapy according to presumed origin, symptom burden, and time course of pain
- Follow guidelines for treatment of pain
- Monitor closely
- Beware medication effects on sleep-related breathing

1. Hurwitz, N. et al. Amyotroph. Lateral Scler. Front. Degener. 2021
2. Abresch, R.T. et al. Am. J. Hosp. Palliat. Care 2002

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Restless legs

- May be caused, unmasked or aggravated by immobilization
- Distinguish from cramps, paraesthesias, neuropathic pain, or venous stasis
- Strictly follow ICSD-3 diagnostic criteria
- Common in ALS, hereditary and other neuropathies

Treatment:

- Serum ferritin > 75 µg/ml
- Dopaminergics, gabapentin/pregabaline, or oxycodon/naloxone according to current guidelines

1. American Academy of Sleep Medicine. International Classification of Sleep Disorders 3rd ed (ICSD-3) 2014
2. Boentert, M.; et a. J. Neurol. Neurosurg. Psychiatry 2014
3. Gemignani, F. et al. Neurology 1999
4. Hattan, E. et al. Neurology 2009
5. Winkelman, J.W. et al. Neurology 2016

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Swallowing – Secretions – Saliva

- Dysphagia common in ALS, OPMD, DMD, SBMA etc.
- Pseudohypersalivation and drooling
- Aspiration risk
- Lower respiratory tract infections

Treatment

- Speech therapy (logopedics)
- Dextromethorphan/Chinidine (off-label)
- Anticholinergic compounds (as and when needed)
- Botulinum toxin injection or radiation of salivary glands
- Cough assistance

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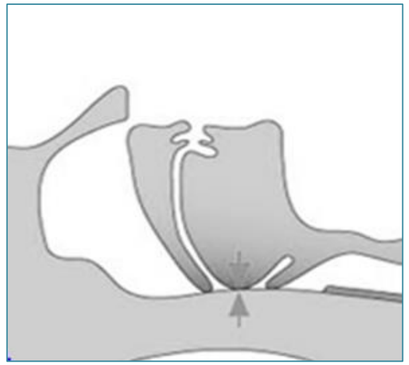
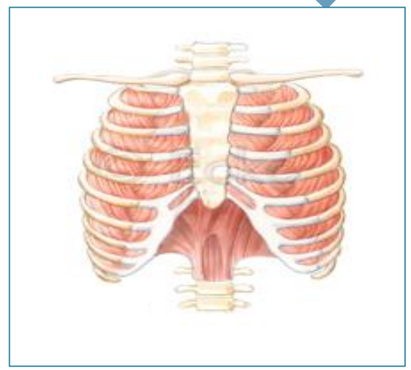
Sleep-disordered breathing





Obstructive sleep apnea

→ Intermittent upper airway collapse

Central sleep apnea

→ Intermittent absence of respiratory drive

Sleep-related hypoventilation

→ Reduced tidal volume and minute ventilation

Symptoms: Sleep disturbances, non-restorative sleep, daytime sleepiness, fatigue

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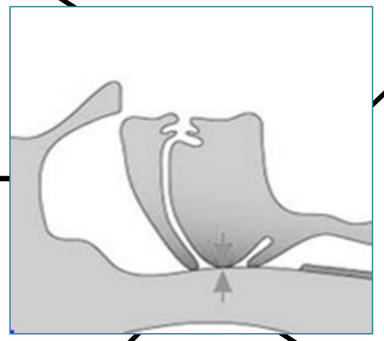
Upper airway in NMD

Pharyngeal anatomy

Disturbance of central respiratory drive (increased loop gain)

Age, male sex, obesity



Decreased pharyngeal muscle tone during sleep (NREM ↓↓/ REM ↓↓↓), Supine body position

Sequelae of NMD:
Pharyngeal weakness & hypotonia
Impairment of pre-inspiratory pharyngeal tonization
Macroglossia (DMD, Pompe)

Osman AM et al., Nature and Science of Sleep 2018

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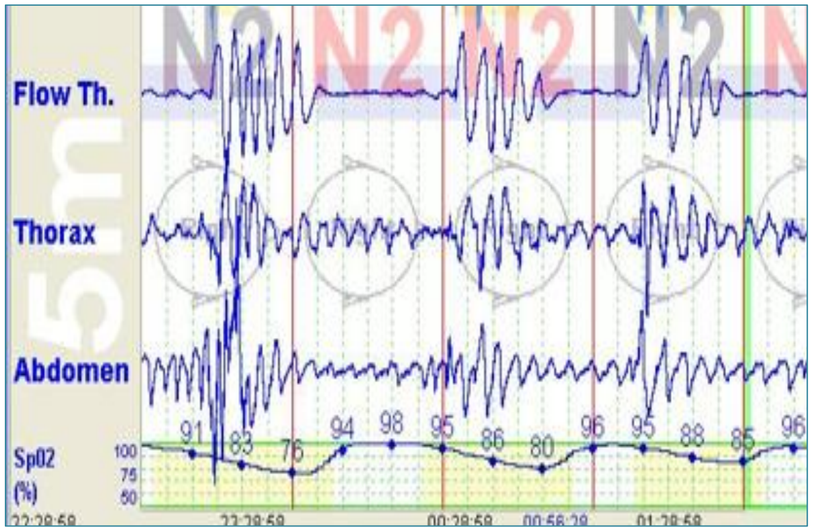
Obstructive sleep apnea (OSA)

Pathophysiology



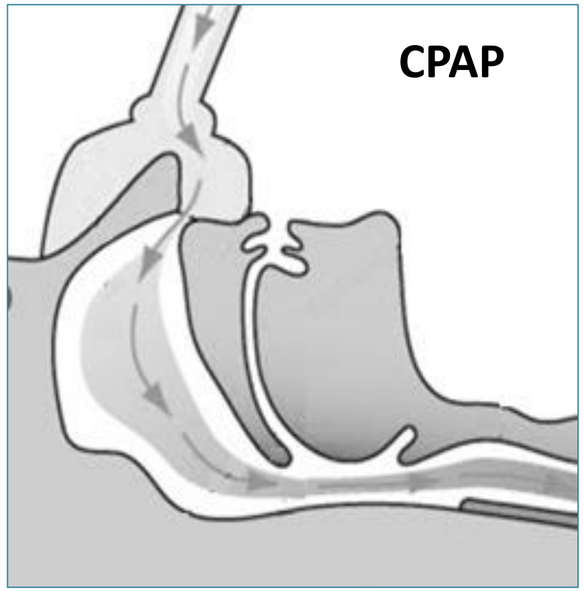
→ **Sleep disruption**
→ **Increases cardiovascular risk and mortality if apnea hypopnea index > 15/h**

Prevalence in NMD

Condition	Prevalence of OSA	Reference
CMT	38%	Boentert et al. 2014
ALS	46%	Boentert et al. 2018
DM1	41-60%	Bianchi et al. 2013 Pincherle et al. 2012 Spiesshoefer et al. 2019
FSHD	55%	Runte et al. 2019
DMD	16-31%	Polat et al. 2012

→ **OSA risk independent of other risk factors**
→ **Beware concomitant hypoventilation!**

Gold standard for treatment



→ **Continous positive airway pressure**
→ **Prevents upper airway collapse**
→ **Only if hypoventilation is ruled out!**

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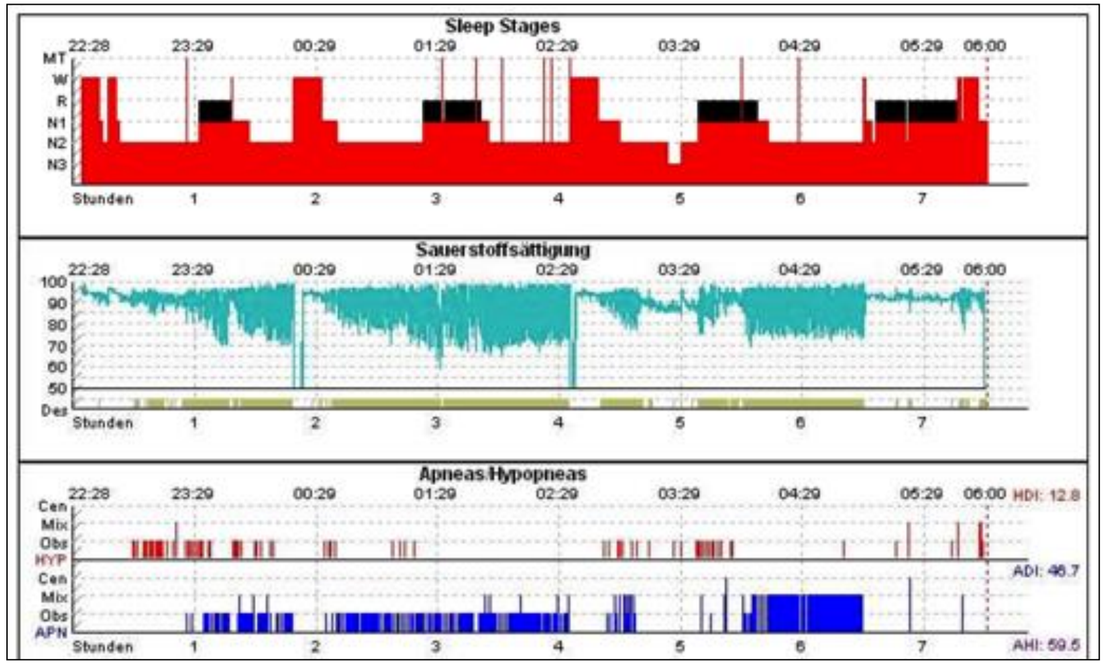
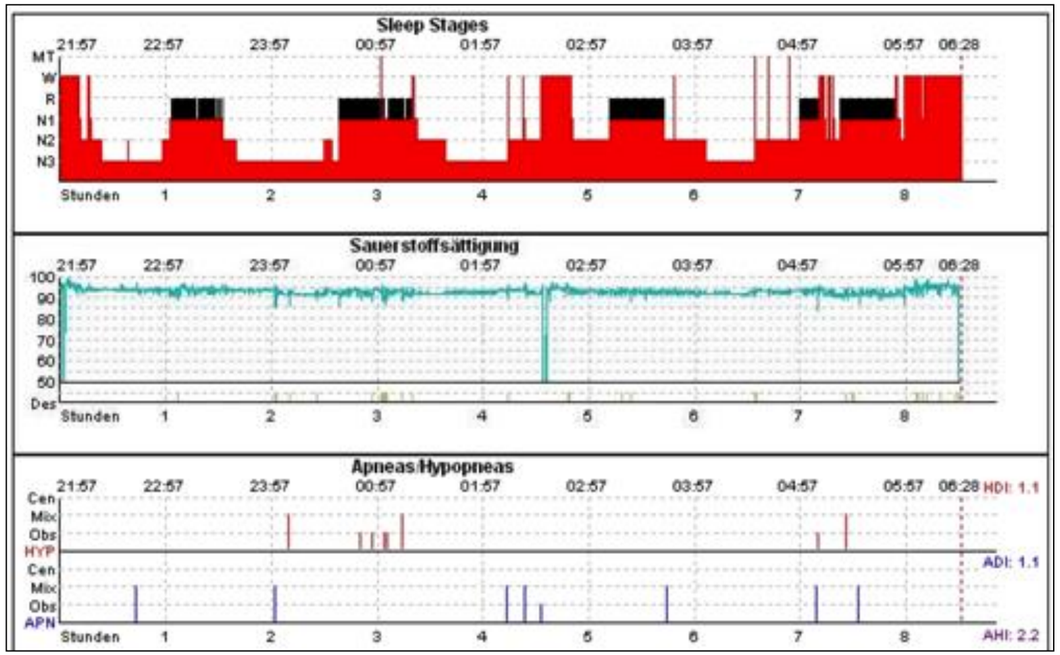
Immediate effects of CPAP



Diagnostic night

- AHI 59.5/h
- ODI 61.2/h
- Arousal index 50.4/h
- N3 percentage 1.5 %



First treatment night

- AHI 2.2/h
- ODI 2.7/h
- Arousal index 11.3/h
- N3 percentage 31.2 %

Male patient with CMT1A, 38 yo, BMI 26

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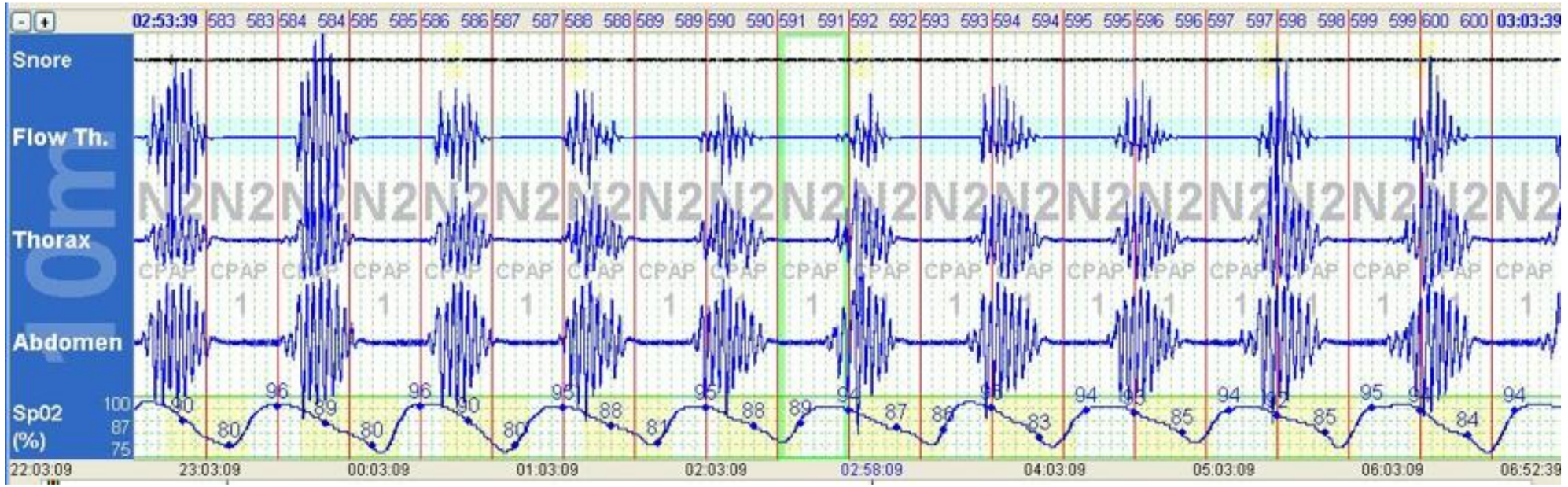
Central sleep apnea (CSA)



Female patient with DM1, 37 yo, BMI 24

→ Intermittent lack of central respiratory drive
→ In people with myotonic dystrophy
→ Related to cerebral white mattter lesions
→ Coincident with OSA and/or sleep-related hypoventilation

→ **Treatment**:
Bilevel positive airway pressure with backup rate = non-invasive ventilation

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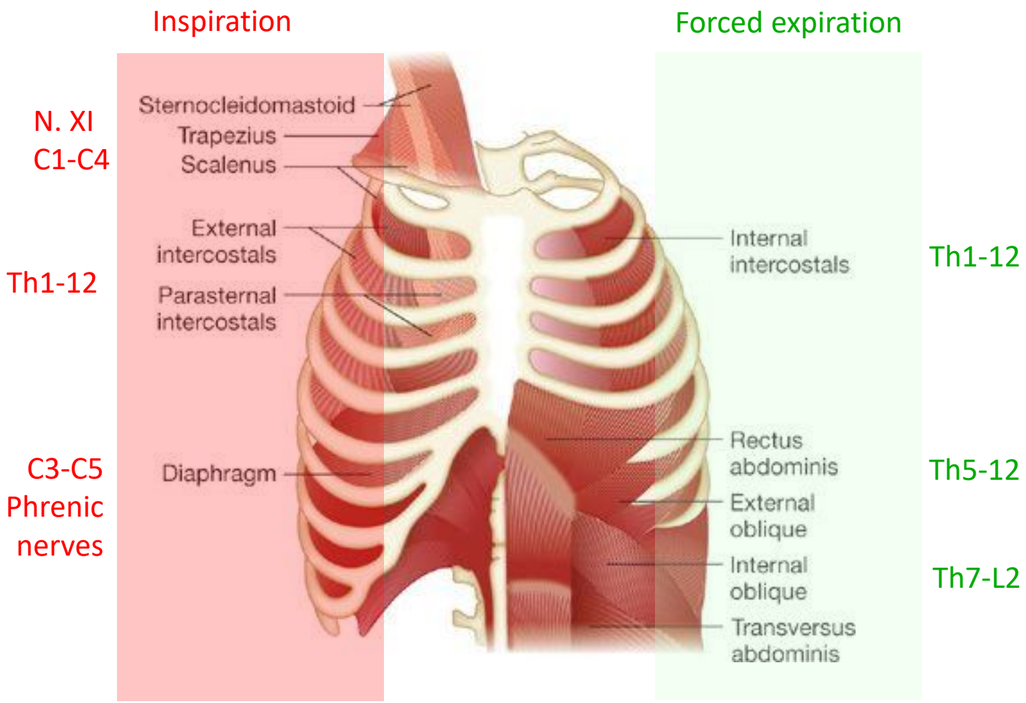
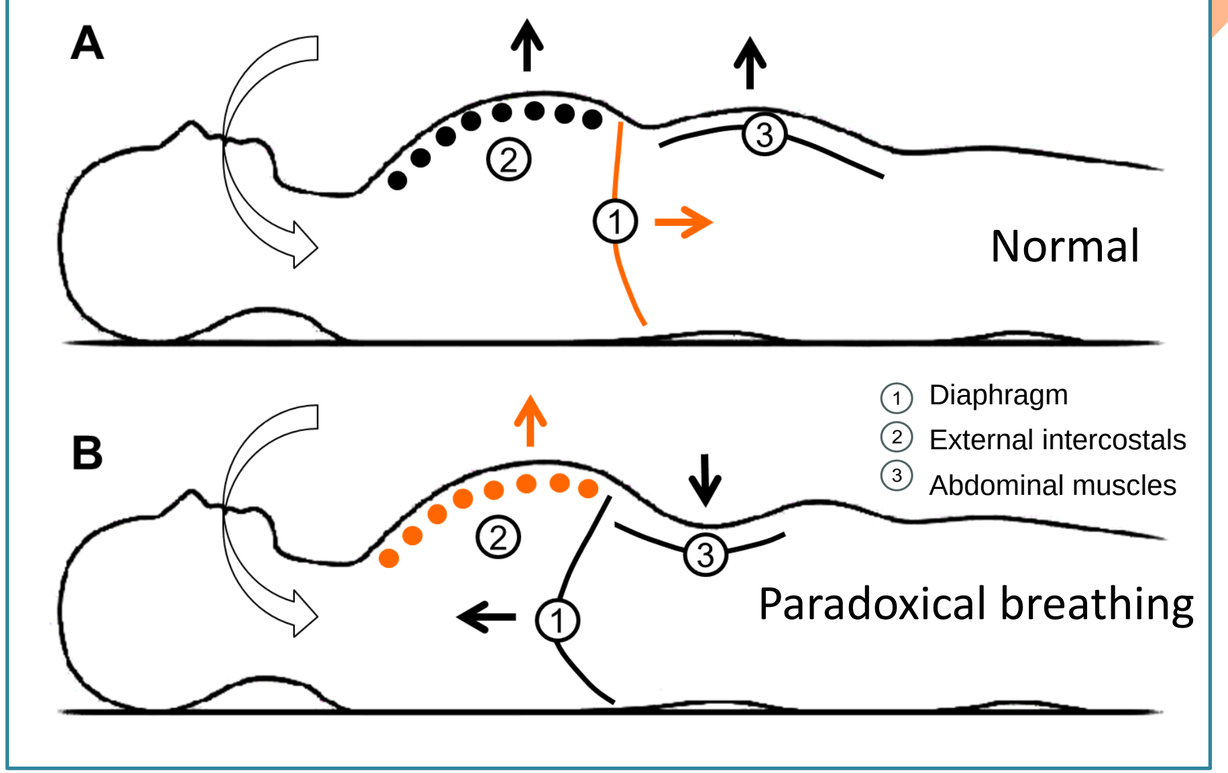
Respiratory muscle weakness





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NMD with respiratory muscle weakness

NEUROGENIC	• Amyotrophic Lateral Sclerosis (ALS) • Spinal Muscular Atrophy I-III • Hereditary Neuropathies • Guillain-Barré syndrome • Phrenic nerve palsies

Critical-illness neuromyopathy / ICU acquired weakness

MYOGENIC	• Muscular dystrophies • Limb girdle muscular dystrophies • Myotonic dystrophy type I • Pompe disease • Congenital myopathies • Myasthenic syndromes

Boentert M, Wenninger S, Sansone V. Curr Opin Neurol 2017

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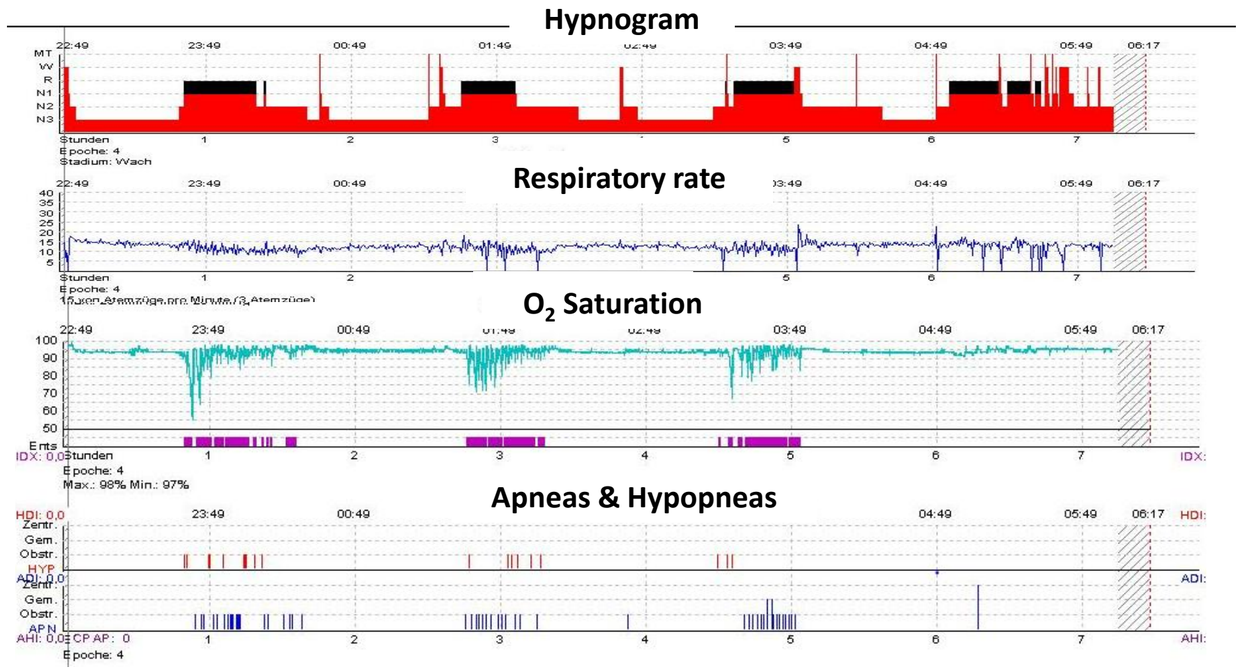
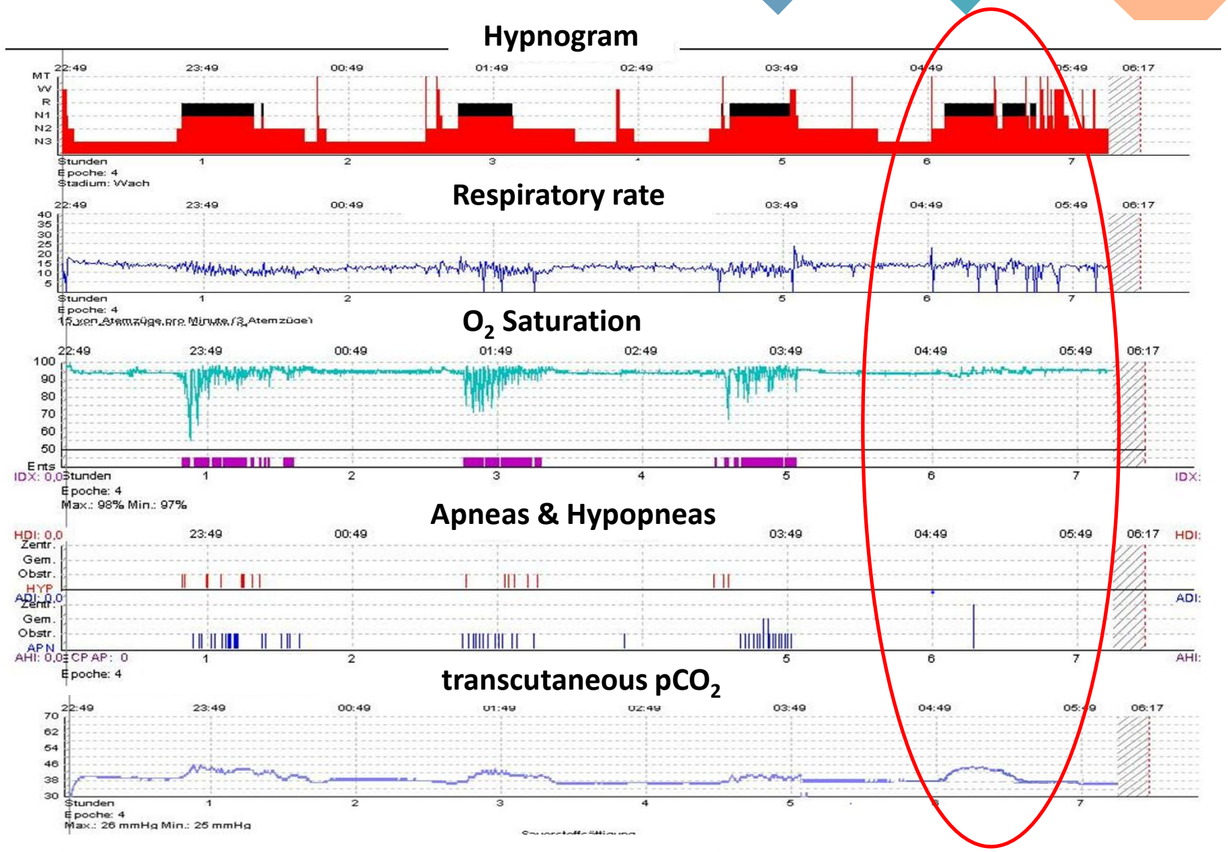
Sleep-related hypoventilation



→ Obstructive events during REM sleep → desaturation



→ Hypoventilation during REM sleep → hypercapnia only

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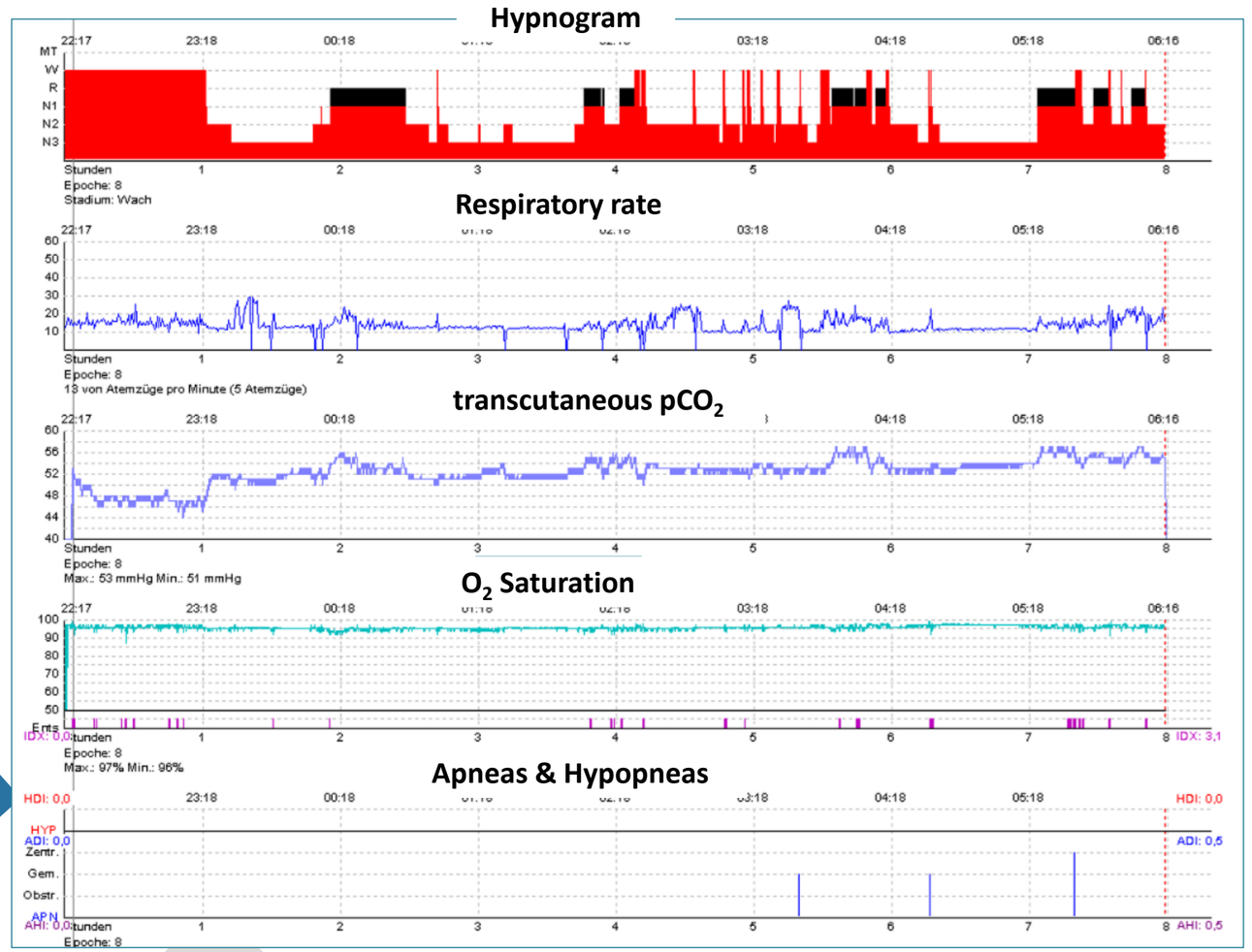
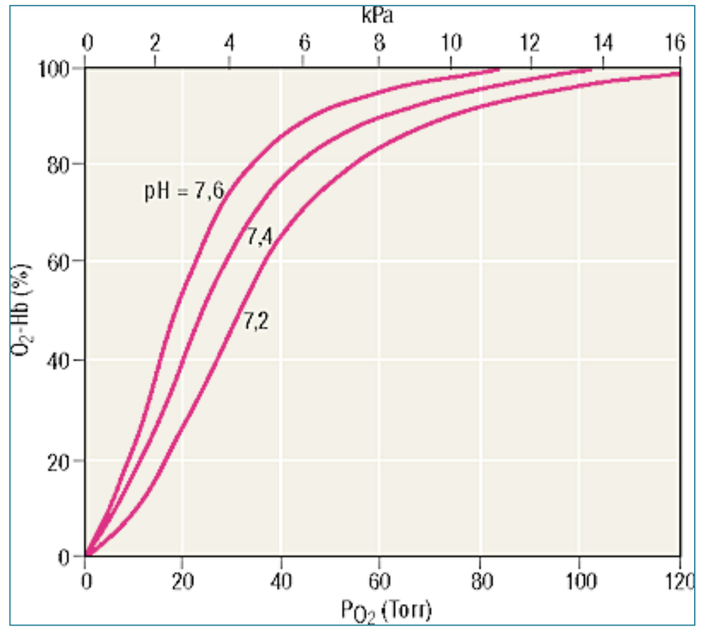
Capnography superior to oxymetry





Sensitivity of oxymetry to detect hypoventlation is only 0,69 in people with NMD and chest wall disease.

Overnight capnography is indispensable for **early diagnosis** of nocturnal hypoventilation.

Georges M et al., Respirology 2016
Boentert M et al., JNNP 2018

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Diagnostic pathway

Method	Parameter	Pros	Cons	Remarks
Signs & symptoms	Sleep disruption Daytime sleepiness Dyspnea	Patients tell and show…	Non-specific or may not be present	Obligatory
	Paradoxical breathing	Easy to test	None	Test if possible
Respiratory muscle function tests	FVC	Bedside test	Global measure of lung function; sensitivity rather low	Standard; monitor regularly
	FVC positional drop	Better than upright FVC only	None	If >20%, nocturnal hypoventilation likely
	MIP (max. insp. pressure)	Bedside test	Special device needed	-
	SNIP (sniff nasal pressure)	Bedside test; MIP surrogate	Special device needed	If mouth closure is weak
Daytime blood gases	pCO_2 Base excess	Relatively easy to obtain	No standard for outpatients	Daytime hypercapnia late; BE > 2 mmol/l predicts nocturnal hypoventilation
Overnight studies	Pulse oxymetry	Widely available	SpO_2 too insensitive	Insufficient
	Polygraphy	Widely available	SpO_2 too insensitive	Insufficient w/o capno
	Polysomnography	Sleep staging possible	SpO_2 too insensitive; costs	Insufficient w/o capno
	Capnography	Highly sensitive	No standard in sleep labs; costs	-

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Non-invasive ventilation (NIV): Indication criteria

	NICE 2016	ERS 2002	DGP 2025	ACCP 2023
Clinical	"symptoms"	"symptoms"	Signs and symptoms of respiratory muscle weakness or sleep-disordered breathing	Fatigue, dyspnea, (morning) headache, witnessed apneas
Daytime	• FVC<50 % w/o symptoms • FVC <80% w/ symptoms • MIP <60 cm H_2O	• FVC< 80% • SNIP <40 cmH2O • morning p_aCO_2>45 mm Hg	• FVC<70% • FVC decline >10% within <3 months • MIP<60 cm H_2O • daytime pCO_2>45 mmHg	• FVC<50 % w/o symptoms • FVC <80% w/ symptoms; • MIP/SNIP <60 cmH_2O • MEP < 40 cmH_2O • pCO_2≥45 mmHg
Nocturnal	-	-	$p_{tc}CO_2$ > 50 mmHg $\Delta p_{tc}CO_2$ ≥ 10 mmHg	SpO_2 ≤ 90% for ≥ 2% of sleep time AHI ≥ 5 /h

→ consensus needed that better includes overnight capnography

1. https://www.nice.org.uk/guidance/qs126/chapter/quality-statement-2-respiratory-assessment-and-noninvasive-ventilation
2. Shneerson JM, Simonds AK. Eur Resp J, 2002 20(2): 480-487
3. Stanzel SB et al., S3 Guideline: Treating Chronic Respiratory Failure with Non-invasive Ventilation,Pneumologie 2025;79(1):25-79.
4. Khan A et al. CHEST, 164, Issue 2, 394 - 413

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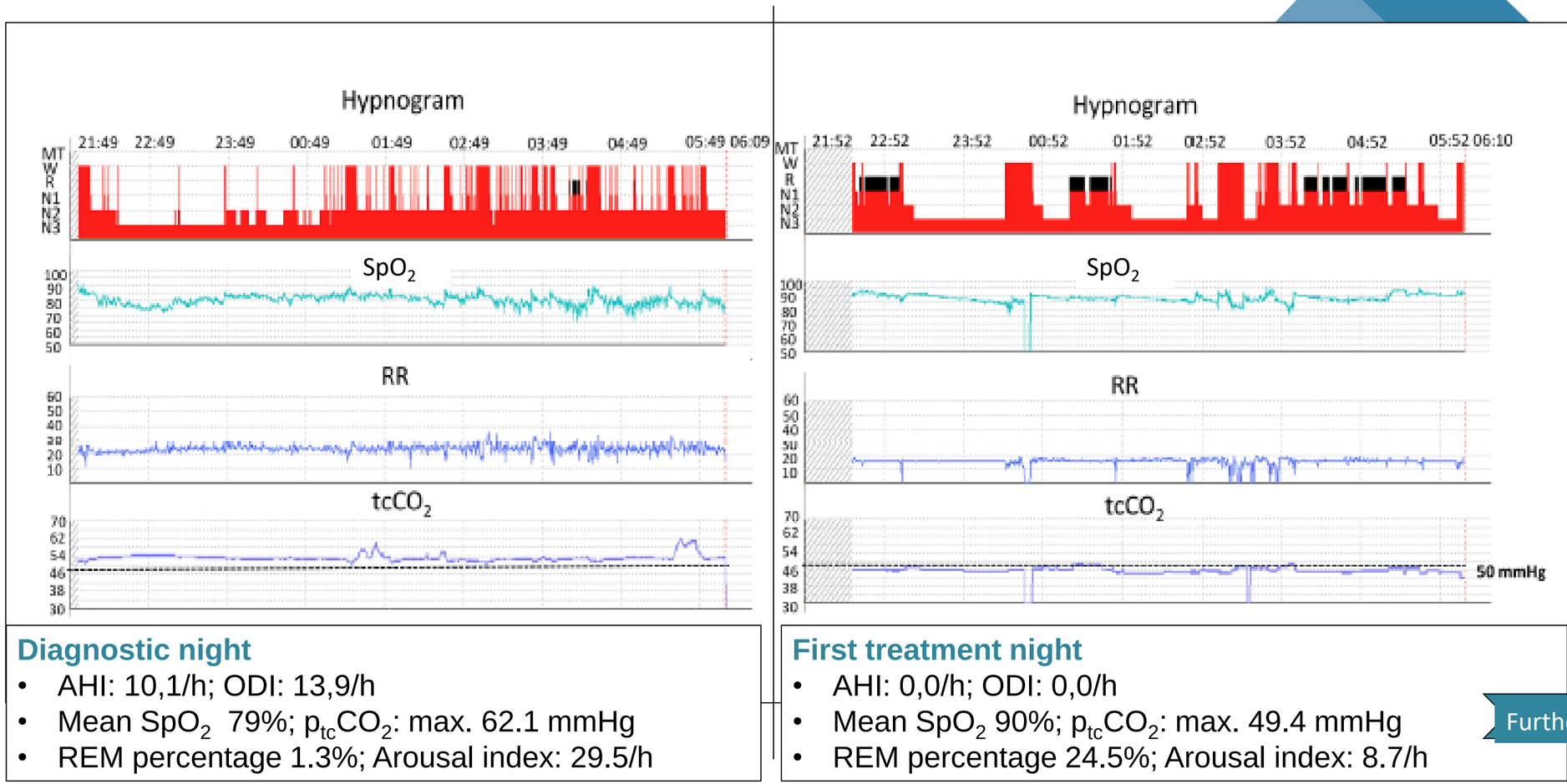
Immediate effects of NIV



Diagnostic night

- AHI: 10,1/h; ODI: 13,9/h
- Mean SpO_2 79%; $p_{tc}CO_2$: max. 62.1 mmHg
- REM percentage 1.3%; Arousal index: 29.5/h

First treatment night

- AHI: 0,0/h; ODI: 0,0/h
- Mean SpO_2 90%; $p_{tc}CO_2$: max. 49.4 mmHg
- REM percentage 24.5%; Arousal index: 8.7/h

Further titration

Female patient with bulbar ALS, 62 yo, BMI 20

→**Improvement of ventilation, alveolar gas exchange, apnea-hypopnea index, oxygenation, and sleep architecture**

→**Improvement of sleep quality**

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NIV: Long-term effects

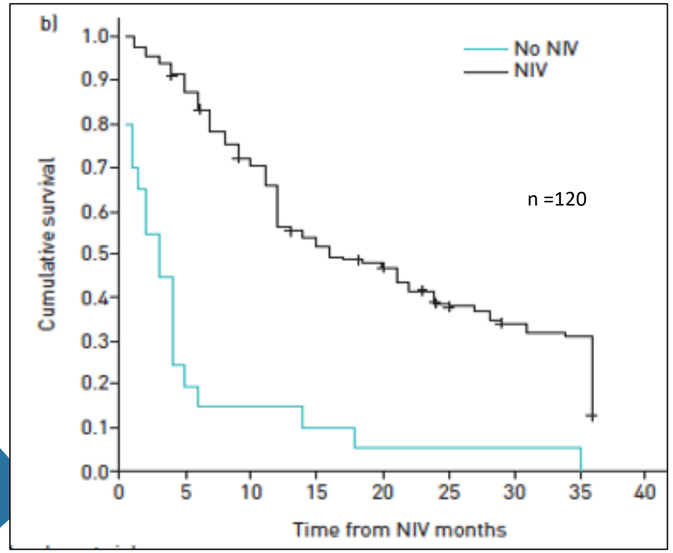
⇑ Sleep quality, daytime performance, ability to participate, quality of life

⇓ Work of breathing, energy consumption, weight loss

⇓ Complications and secondary diseases

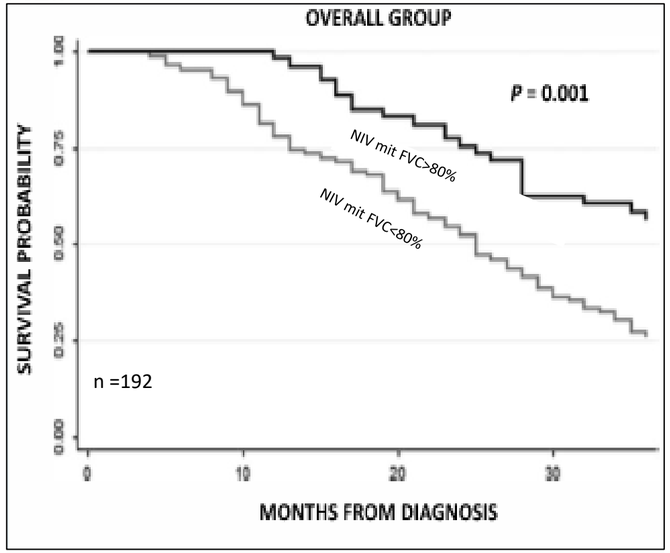
⇑ Overall prognosis and survival time

ALS



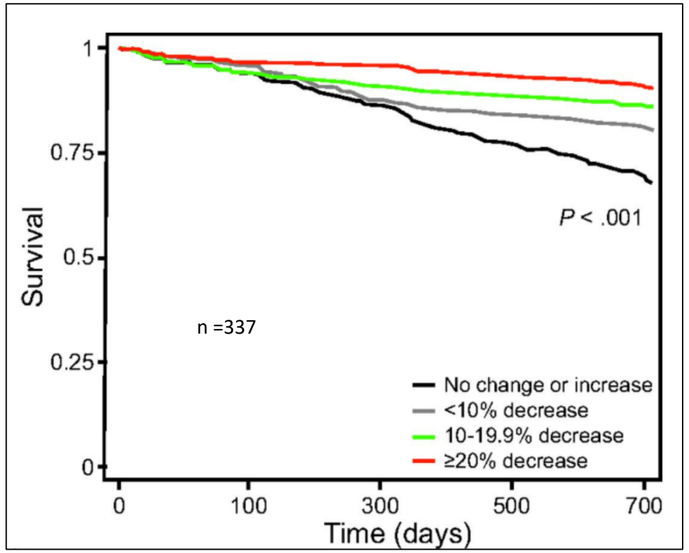
→ NIV prolongs life span

ALS



→ Early NIV is meaningful

Various NMD



→ Normocapnia counts

Sancho J et al. (2018), ERJ Open Res; Vitacca M et al. (2018), Eur J Neurol; Jimenez JV et al. (2023), Resp Care

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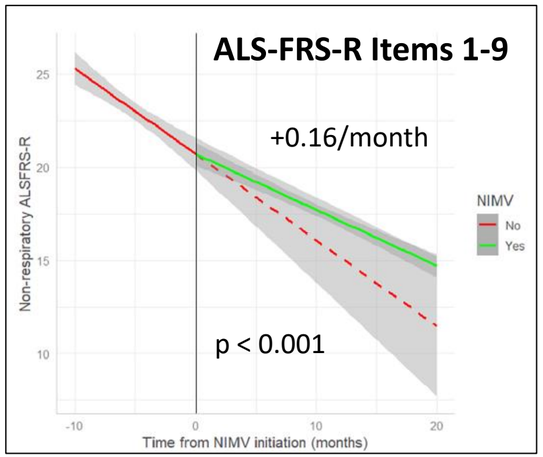
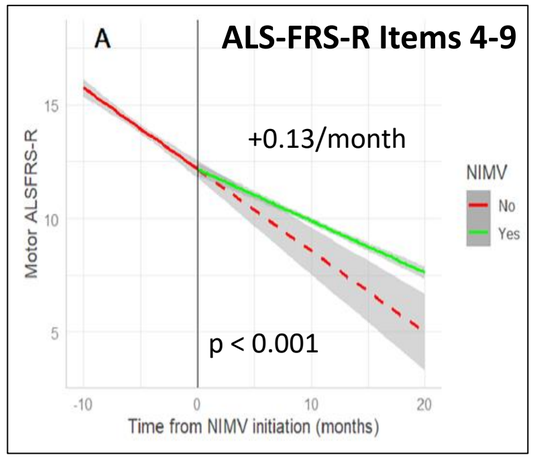
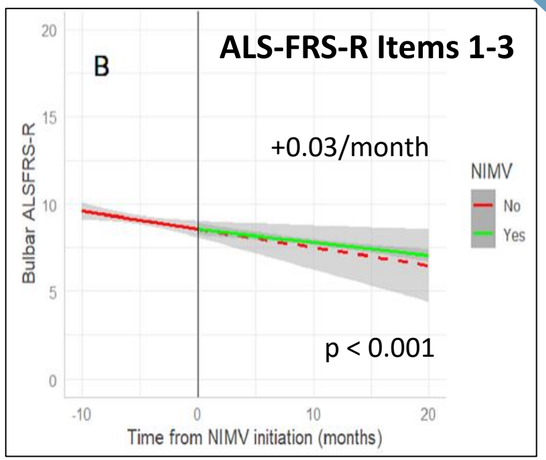
NIV effects in ALS

n = 448

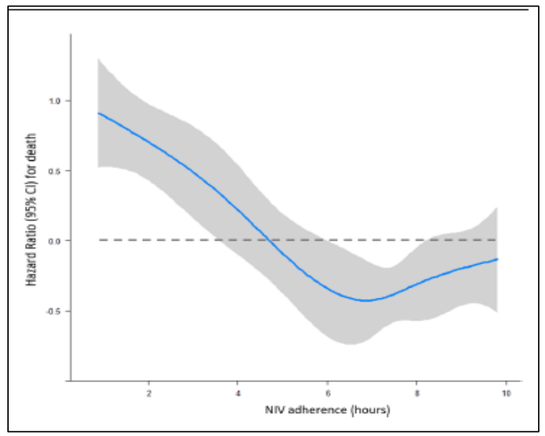


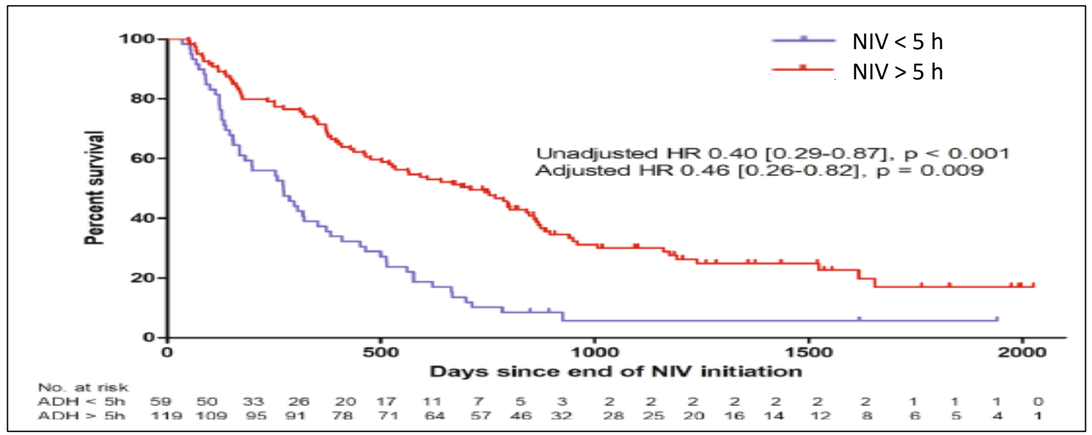




→**NIV attenuates motor function loss**

n = 178





→**Adherence is crucial**

Grassano M, Ann Neurol 2024;00:1–6

Reginault T et al. Journal of Neurology 2024; 271:5590–5597

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Weakness of cough

Causes

- Severe inspiratory muscle weakness
- Expiratory muscle weakness
- Weakness of glottic closure

Peak Flow Meter
(Peak Cough Flow)

Treatment

- PCF > 350 l/min → normal/keep monitoring
- PCF 270-350 l/min → closer monitoring
- PCF 160-270 l/min without mucus retention
  → manually assisted coughing/air stacking
- PCF < 160 l/min or 160-270 l/min with mucus retention
  → mechanical insufflator-exsufflator
  → secretolytic measures if needed

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Wrap-up: In NMD…

… sleep disturbances are common & meaningful

… multifaceted & multifactorial

… immobility alone may take its toll

… pain, cramps, spasticity and RLS may play a role

… obstructive sleep apnea is very common

… central sleep apnea occurs in DM1 and mitochondrial disease

… respiratory failure starts with sleep-related hypoventilation

… capnography beats oximetry

… CPAP is for isolated OSA, NIV for CSA and hypoventilation

… NIV benefits depend on timing & adherence

… beware cough assistance & management of secretions

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Thank you for your attention!

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