Centraal slaapapneu (CSA)

en

hartfalen

Dr. Hennie Janssen, longarts –somnoloog

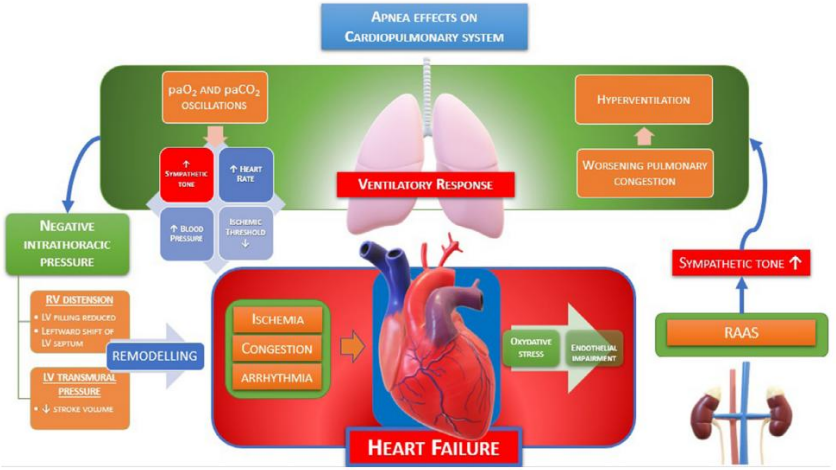
Kempenhaeghe | Centrum voor Slaapgeneeskunde Kempenhaeghe

Alle kennis.
Alle aandacht.

Disclosure belangen spreker	
(Potentiële) belangenverstrengeling	Zie hieronder
Voor bijeenkomst mogelijk relevante relaties	Congresvoordrachten voor VIVISOL Nederland BV en Air Liquide Health Care. Deelgenomen aan research met Philips binnen The Eindhoven MedTech Innovation Center (e/MTIC)
• Honorarium of andere (financiële) vergoeding[3]	Fee paid to institution

Inhoud presentatie

- Hartfalen
- Ventilatie tijdens de slaap
- Centraal slaapapneu in hartfalen
  - Pathofysiologie
  - Diagnose
  - Prevalentie
  - Behandeling
- Take home message



Piccirillo, F. Am J Cardiol 2023

Hartfalen

ESC European Society of Cardiology
European Heart Journal (2021) 42, 3599–3726
doi:10.1093/eurheartj/ehab368
ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Table 3 Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction

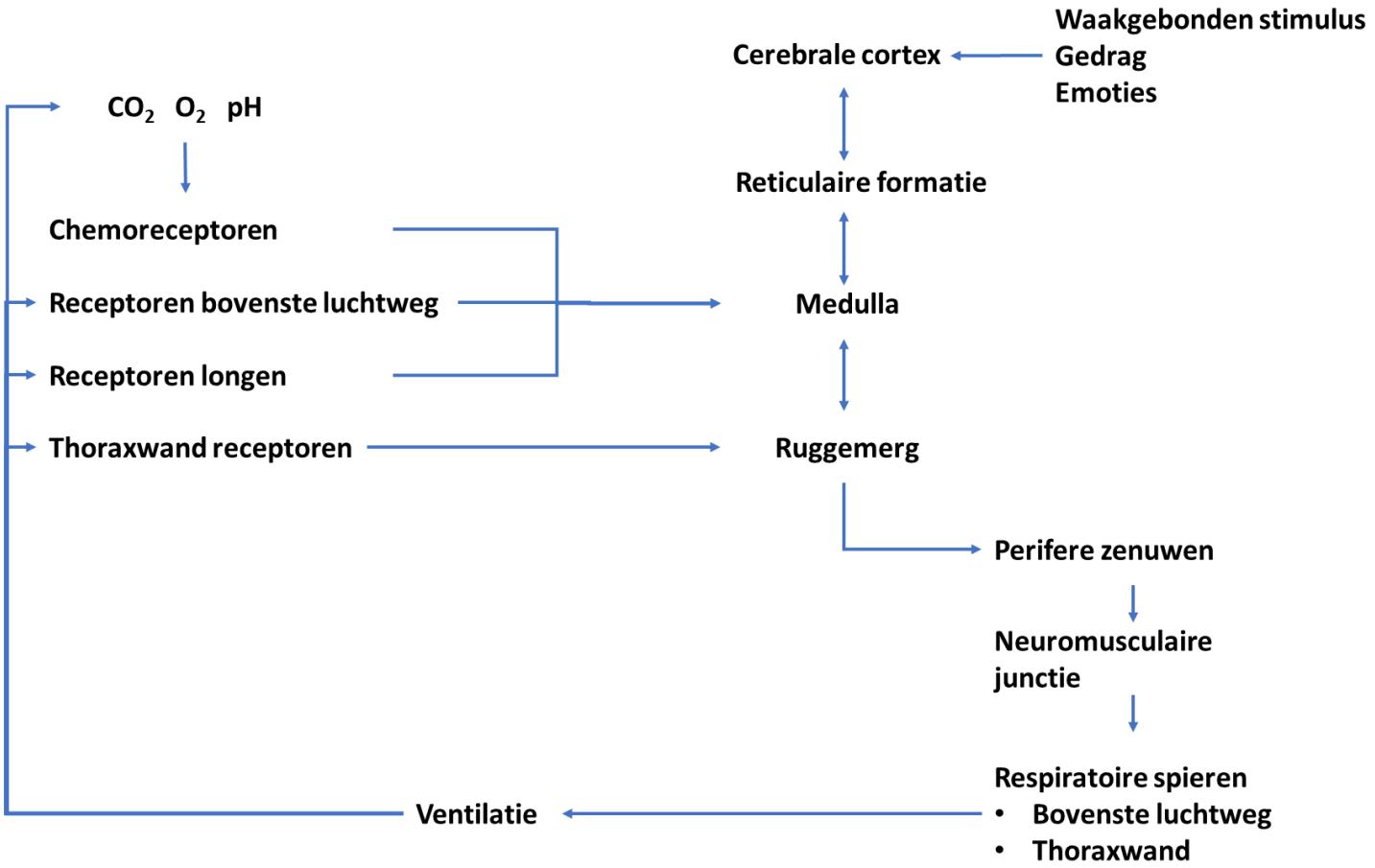
Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

<u>Prevalentie hartfalen:</u>

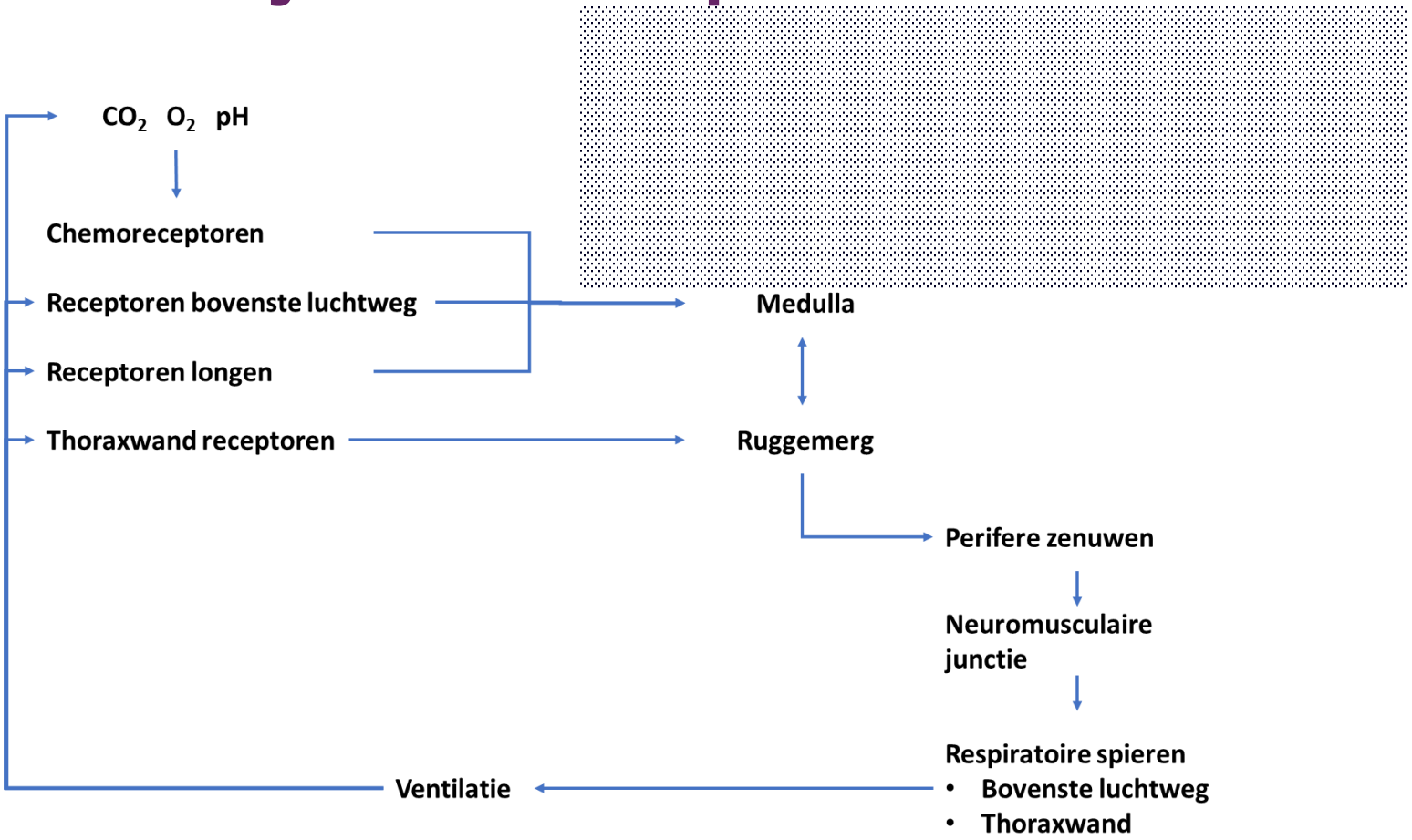
- < 55 jr ~1%; > 70 jr >10%
- Op polikliniek cardiologie: HFrEF 60%, HFmrEF 24%, HFpEF 16%

<u>Mortaliteit:</u> Tot 67% < 5 jr na diagnose

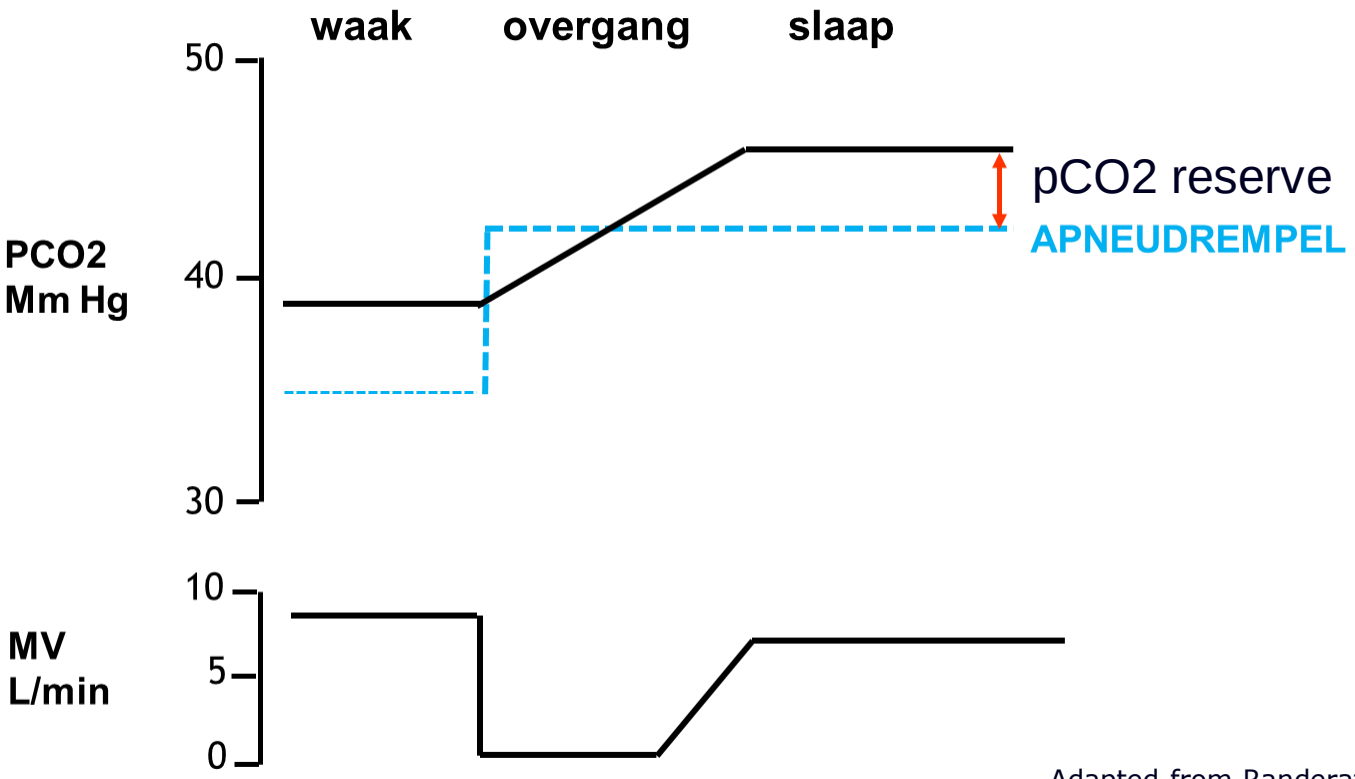
Ventilatie tijdens waak



Ventilatie tijdens de slaap

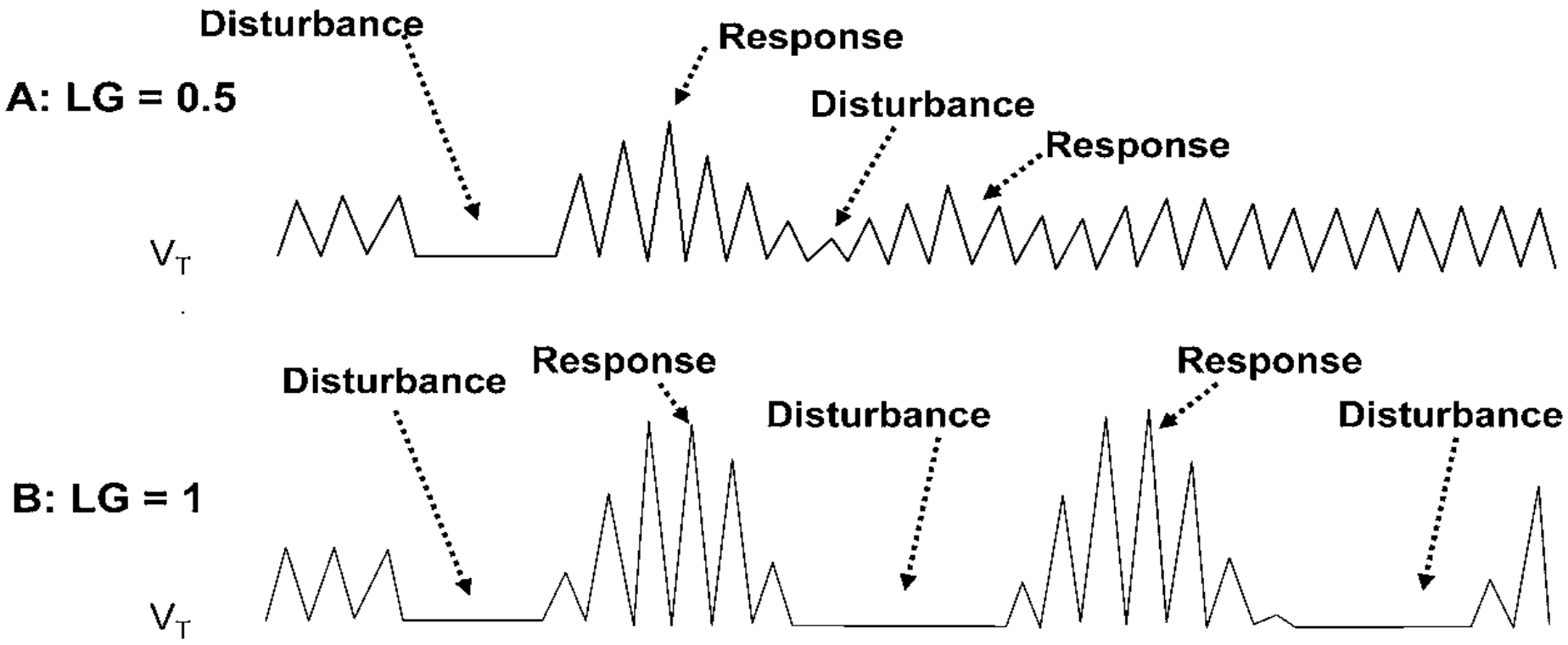


Apneudrempel



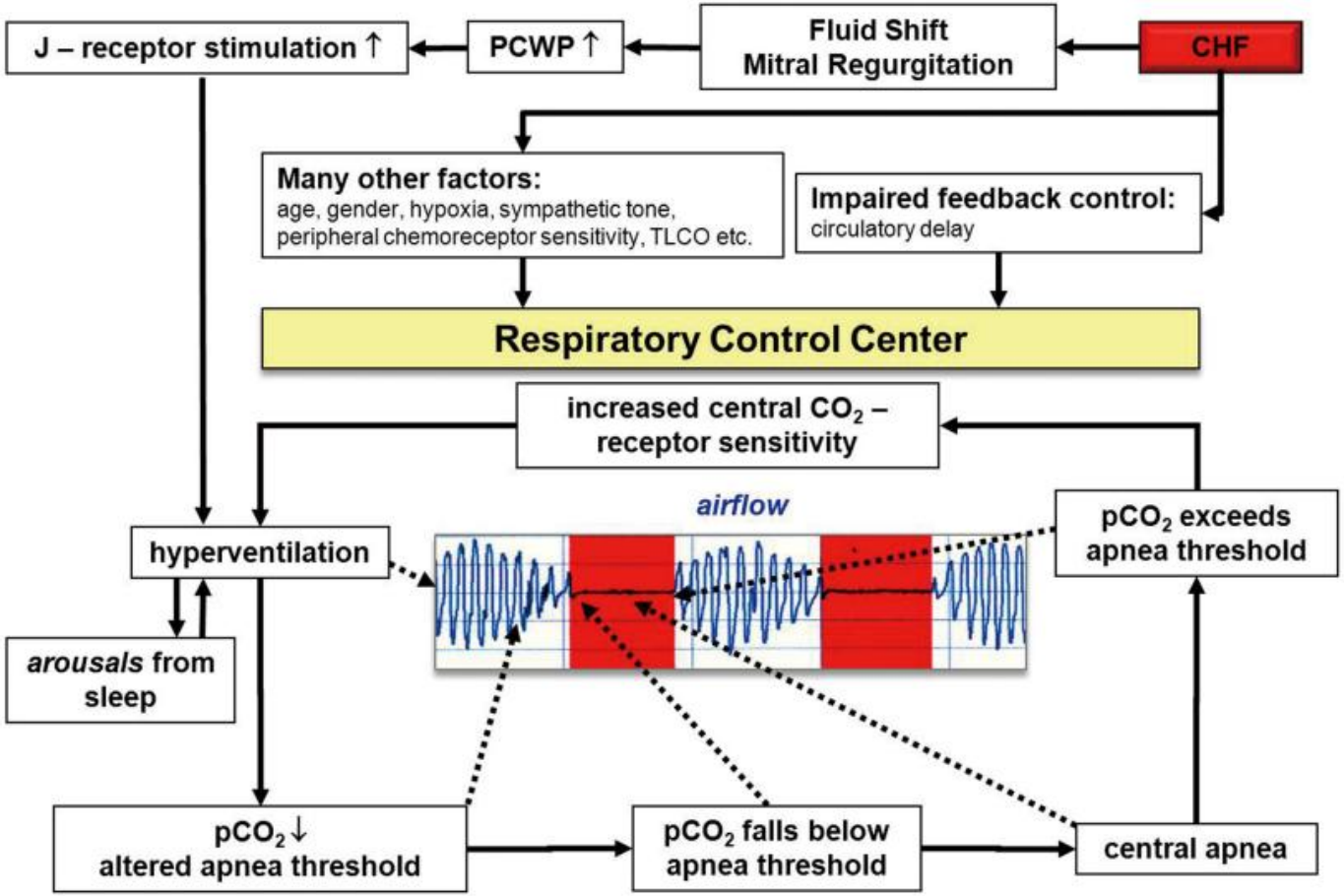
Adapted from Randerath, WJ.Sleep Medicine Textbook. 2021

Loop gain



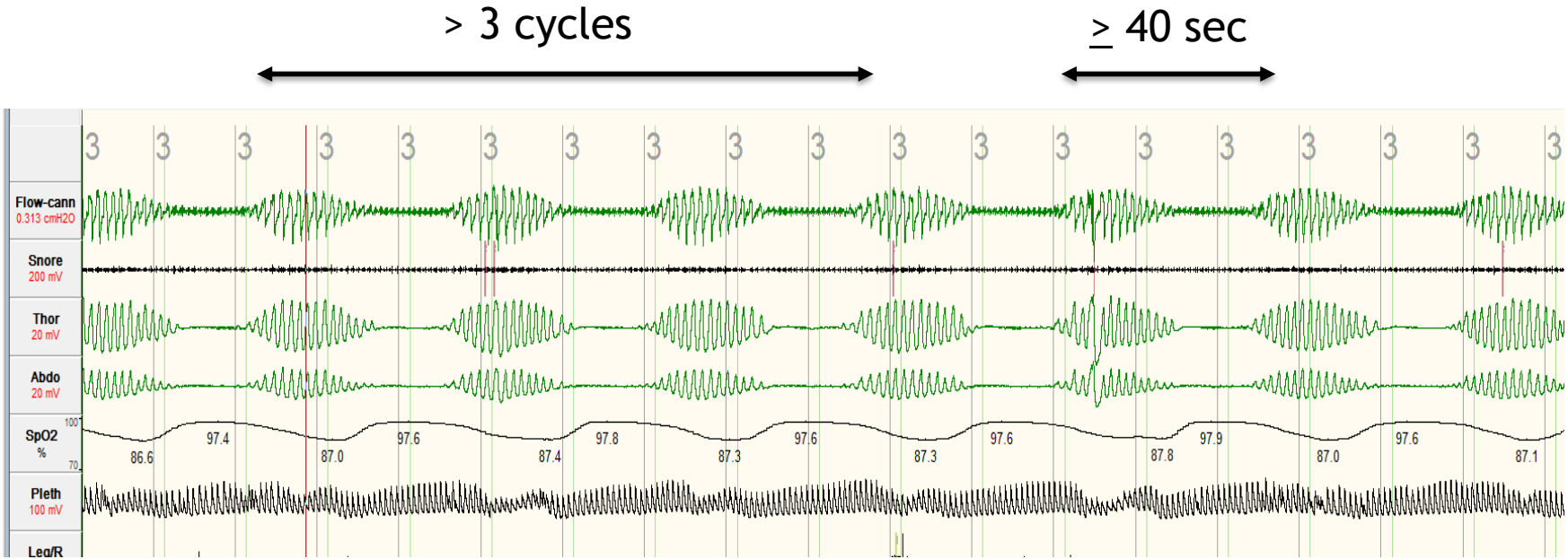
White DP, Am J Respir Crit Care Med 2005

Pathofysiologie CSA in hartfalen



Oldenburg O. Circ. J. 2012

Cheyne Stokes breathing (CSB)/ Periodic breathing with central apnea



AHI ≥ 5/h. Registered sleep ≥ 2 hours

Bron: AASM scoringsmanual

Central sleep apnea with CSB, criteria

(A or B) + C-E must be met:

A. The presence of one or more of the following
    1. Sleepiness
    2. Difficulty initiating or maintaining sleep or nonrestorative sleep.
    3. Awakening short of breath
    4. Witnessed apneas.

B. The presence of atrial fibrillation/flutter, congestive heart failure, or a neurological disorder.

C. Polysomnography (during diagnostic or positive airway pressure titration) shows all the following:
    1. Five or more central respiratory events (central apneas or central hypopneas) per hour of sleep.
    2. The total number of central apneas plus central hypopneas is > 50% of the total number of apneas and hypopneas.

D. The pattern of ventilation meets criteria for Cheyne-Stokes breathing

E. The disorder is not better explained by another current sleep disorder, medication (e.g. opioids) or substance use.

ICSD-3-TR, 2023

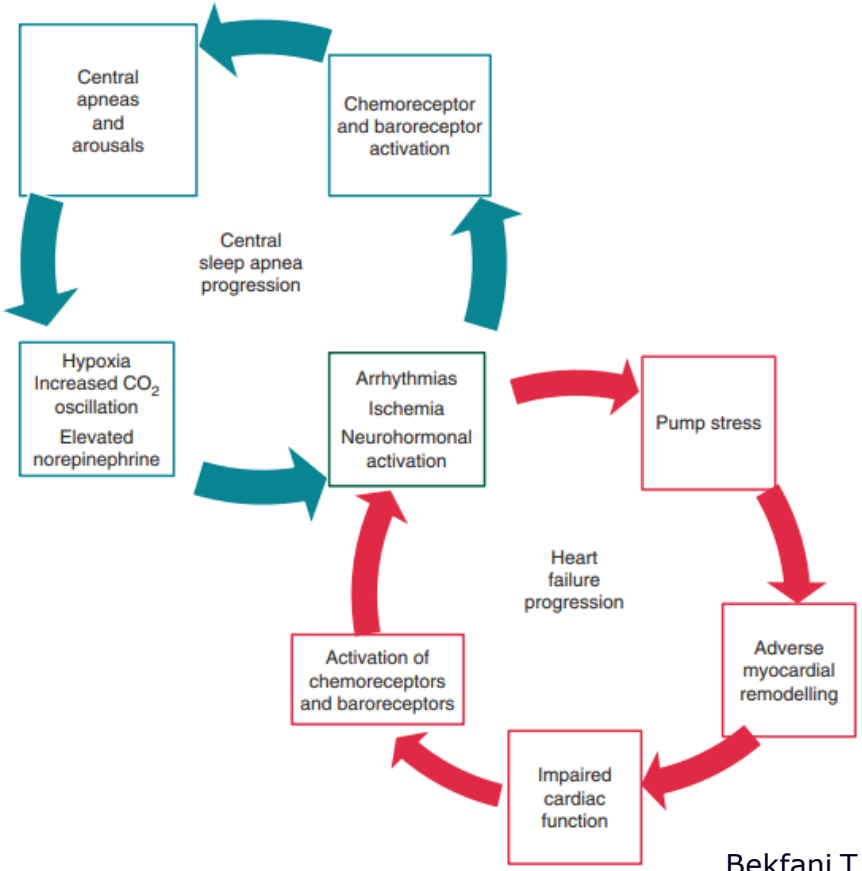
Prevalentie CSA

TABLE 1 Epidemiology of central sleep apnoea (CSA) in specific subpopulations [140]

Condition	Prevalence (%)	References
Idiopathic CSA	4–7	[8, 30]
Chronic heart failure		
Asymptomatic left ventricular systolic dysfunction	55	[36]
Preserved ejection fraction	23–27	[33, 36]
Reduced ejection fraction	34–69	[33, 38, 39]
Stroke	8–12	[46, 47]
Pulmonary hypertension	39	[2, 49]
Chronic kidney disease	10	[50, 51]
Drug-induced CSA		
Opioids	24	[59]
Methadone	30	[60]
Treatment-emergent CSA	10–25	[60]

Eur Respiratory Review. Randerath W, et al. 2024

CSA en hartfalen: interactie

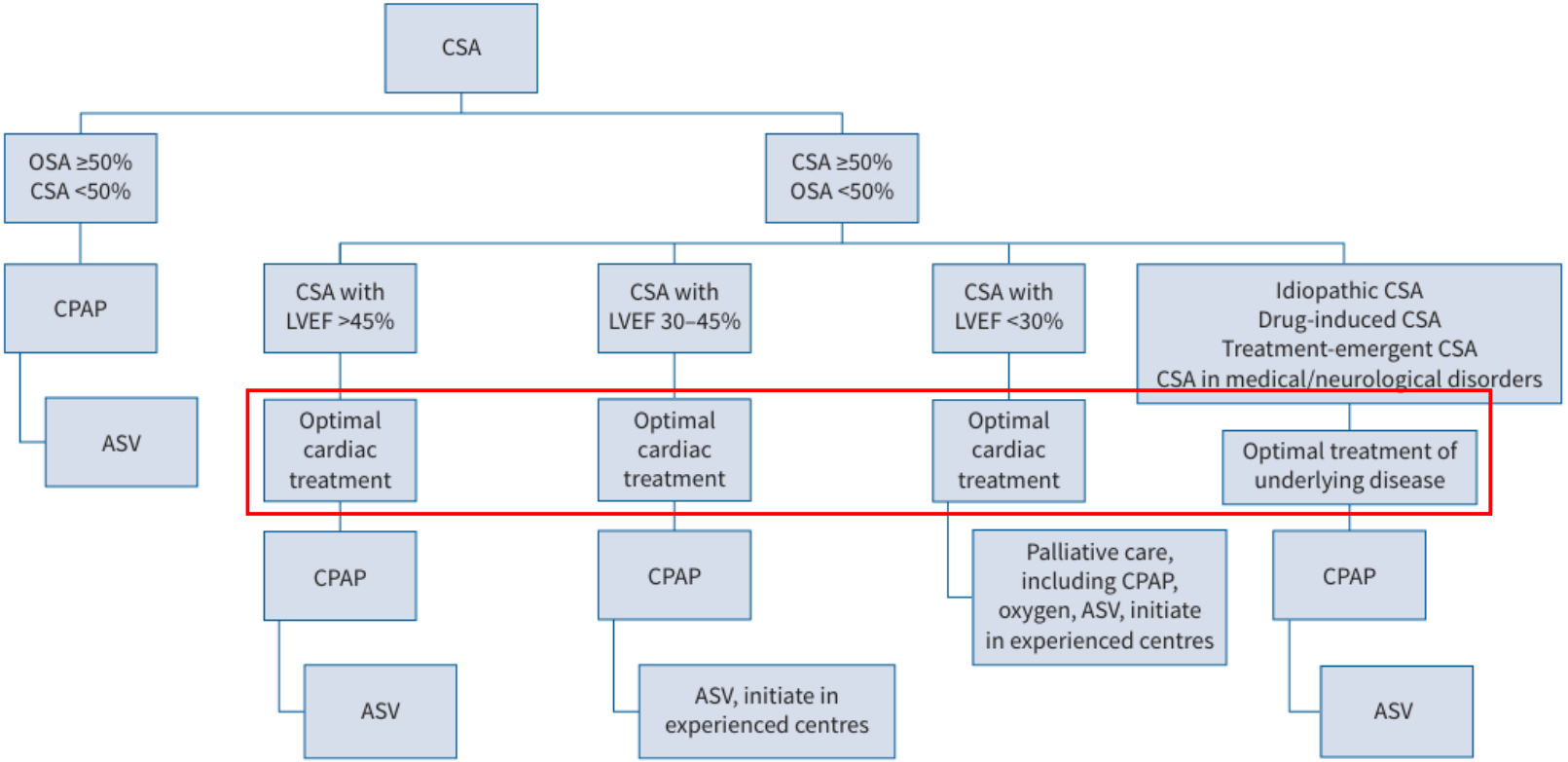


Prevalentie CSA in HF

- HFrEF 25-40%
- HFpEF 18-30%

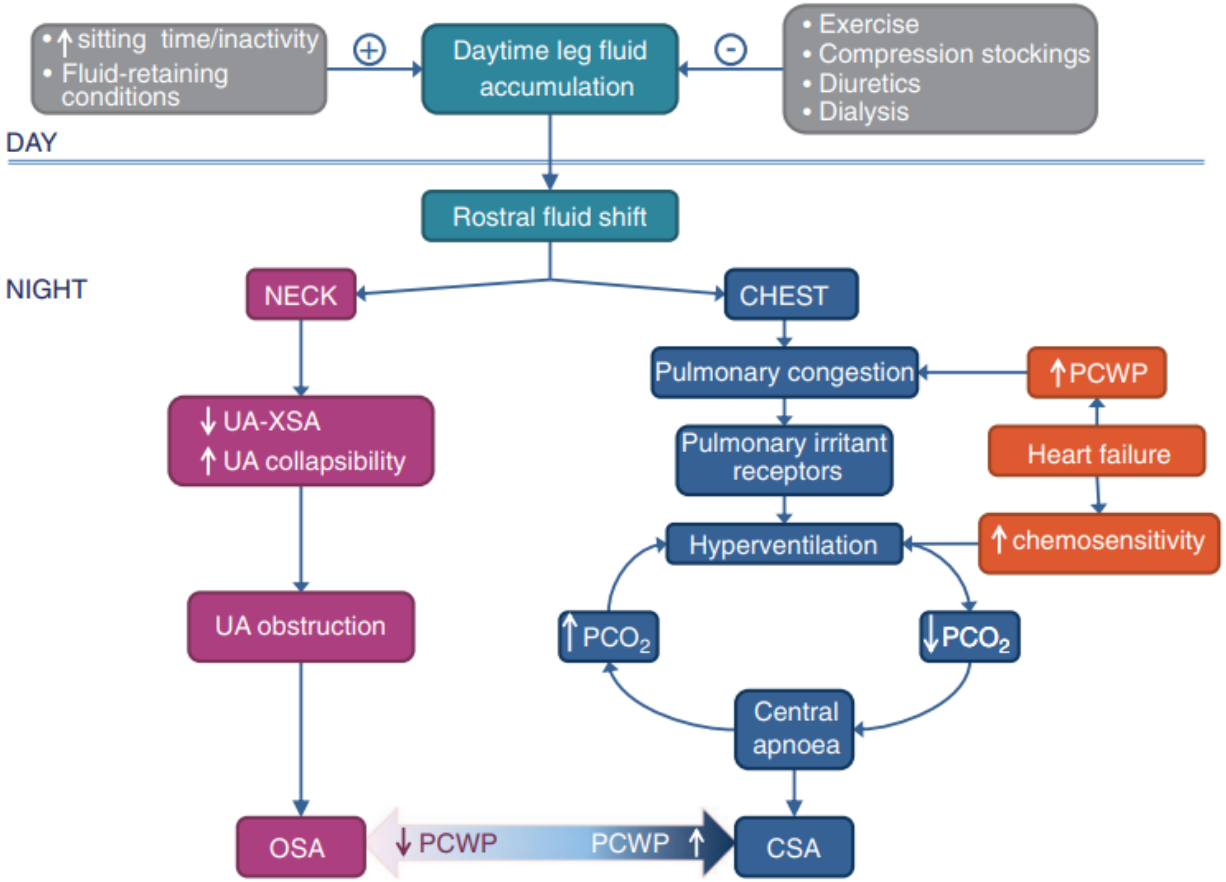
Bekfani T, Europace 2016

ERS/ESRS TF statement (geen guideline) 2025



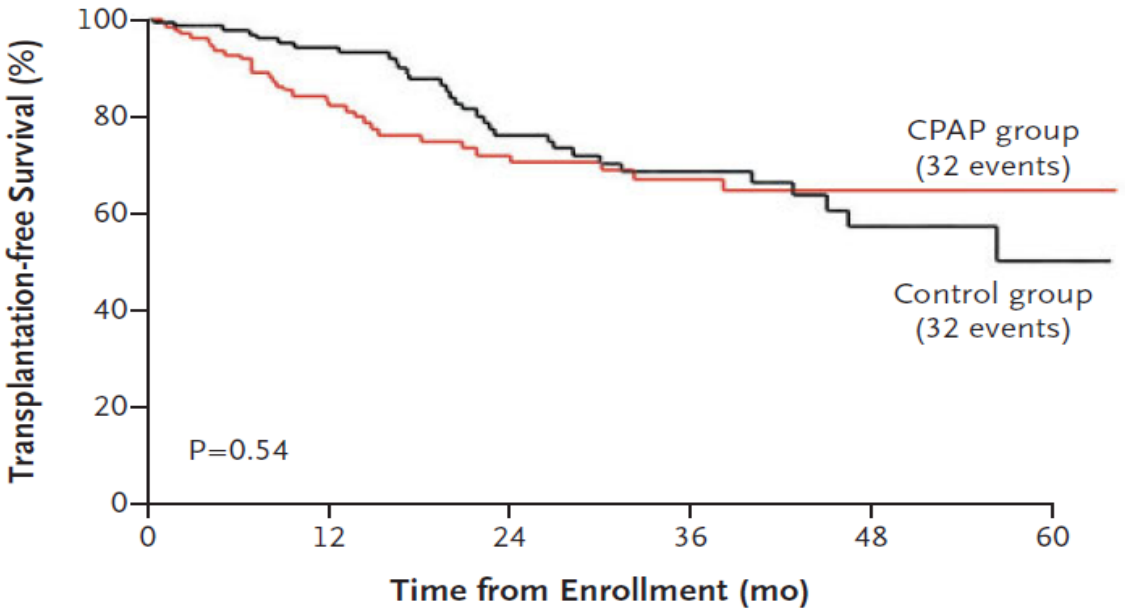
Randerath WJ, et al. Eur Respir J 2025

Voorkomen van fluid shift



White LH, Bradley TD. J Physiol 2013

CPAP



No. at Risk

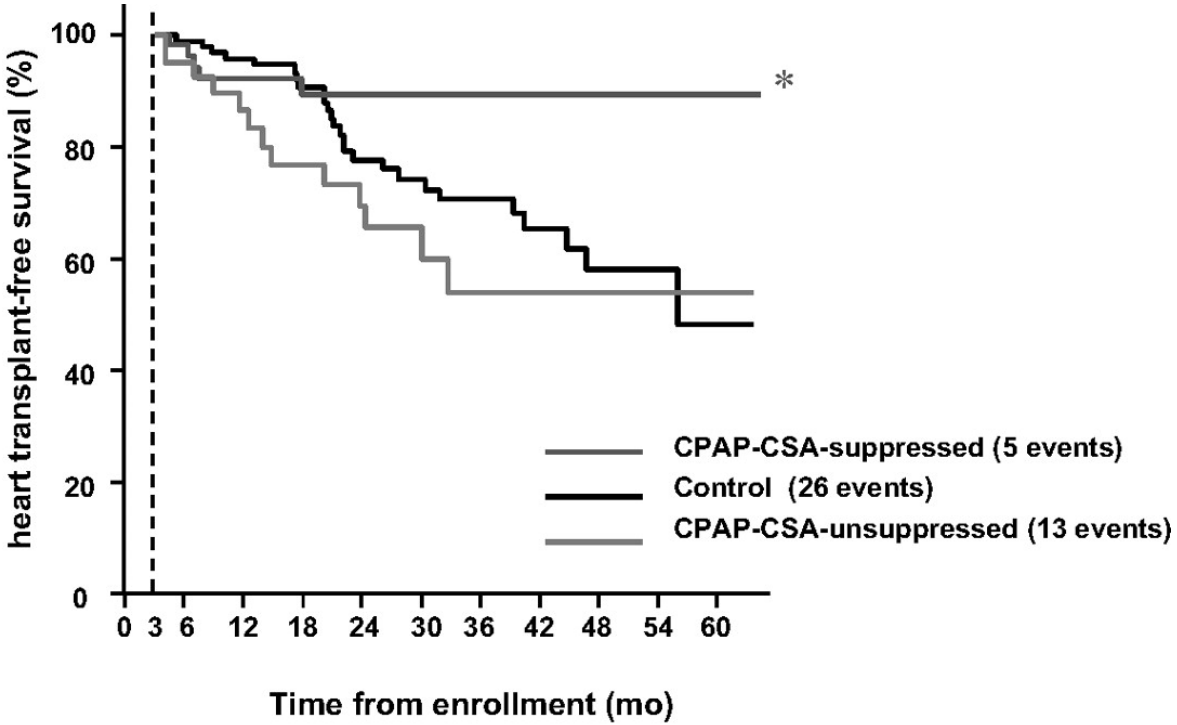
CPAP group	128	104	79	59	49	42	33	24	20	12	6
Control group	130	117	96	79	59	46	37	27	19	12	4

CANPAP trial

- N= 258
  - •HF NYHA II - IV
  - •LVEF < 40%
- CPAP vs controle
- AHI ⇓ 53%
- Voortijdig gestopt

Bradley TD et al. N Engl J Med 2005

CPAP



Arzt M et al. Circulation 2007

CANPAP

- PostHoc, 3mnd
- 57% AHI < 15/u
  - Betere LVEF
  - Betere survival

Conclusie

- Respons in ~ 50%
- AHI ⇓ ~50%

Zuurstof

Study	Pts	NOT		AHI (events/h)		
Author, year	N	Duration	L/min	Baseline	NOT	*p*
Hanly 1989 [23	9	One night	2–3	30.0 ± 4.7	18.9 ± 2.4 (−37%)	<0.01
Walsch 1995 [24	7	One night	2	32 ± 7	23 ± 4 (−28%)	<0.05
Franklin 1997 [25	16	One night	1–5	37.1 ± 0	8.6 ± 0 (−77%)	<0.01
Krachman 1999 [26	9	One night	2	44 ± 9	18 ± 5 (−59%)	<0.001
Javaheri 1999 [27	36	One night	2–4	49 ± 19	29 ± 29 (−41%)	0.0001
Teschler 2001 [28	14	One night	2	44.5 ± 3.4	28.2 ± 3.4 (−37%)	<0.001
Krachman 2005 [30	10	One night	2	57 ± 61	9 ± 11 (−84%)	<0.05
Suzuki 2006 [32	15	One night	3	20 ± 5	6.4 ± 2.1 (−68%)	<0.05
Bordier 2014 [37	19	One night	3	40.5 ± 10.7	26.4 ± 1.6 (−35%)	<0.0001
Andreas 1996 [38	22	One week	4	26 ± 24	10 ± 9 (−62%)	<0.001
Staniforth 1998 [39	11	One month ("long term")	2	37.8 ± 3.9	24.9 ± 3.7 (−34%)	0.01
Krachman 2005 [30	10	One month	2	57 ± 61	12 ± 17 (−79%)	<0.05
Campbell 2012 [36	7	Two months	2	63 ± 30	19.4 ± 15.7 (−79%)	<0.05
Arzt 2005 [29	10	Three months	2	28.8 ± 3.2	8.7 ± 4.1 (−70%)	0.02
Sasayama 2006 [31	25	Three months	3	21.0 ± 10.8	10.0 ± 10.6 (−52%)	<0.001
Toyoma 2009 [34	10	Three months	3	26.1 ± 9.1	5.1 ± 3.4 (−80%)	<0.01
Shigemitsu 2007 [33	18	Four months	2–3	33.1 ± 11.3	6.23 ± 3.16 (−81%)	0.0004
Bordier 2014 [37	16	Six months	3	36.8 ± 2.6	18.3 ± 2.4 (−50%)	<0.0001
Sasayama 2009 [35	21	12 months	3	19.0 ± 12.3	9.0 ± 8.4 (−53%)	<0.01

Conclusie

- Kleine studies
- Heterogene populatie
- Korte follow up
- Respons in ~ 50%
- AHI ⇓ ~50%

Bordier P, et al. Sleep Medicine 2016

LOFT-HF studie

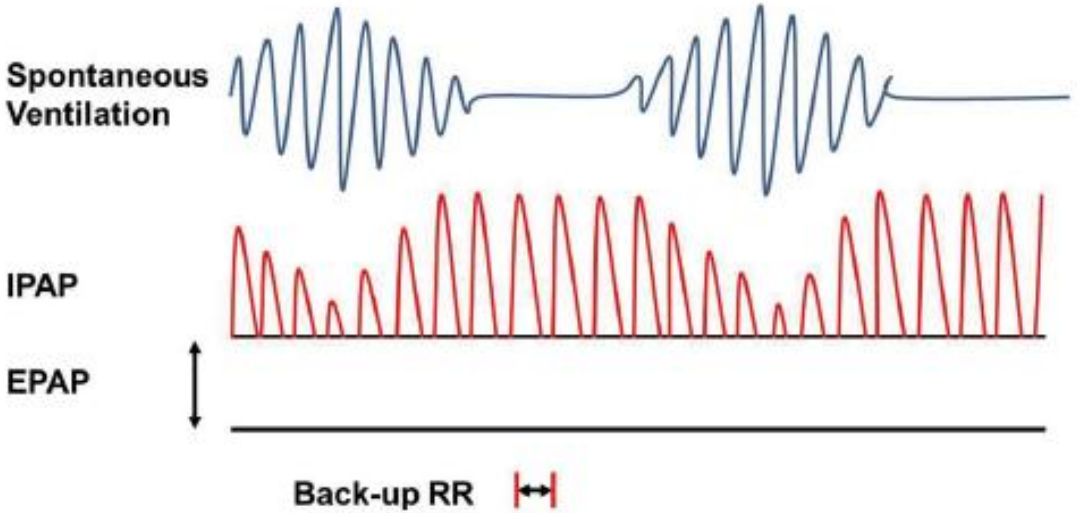
- RCT, dubbel blind, Zuurstof vs Sham
- HFrEF ptn behandeld volgens cardiale richtlijnen. Doel N=858
- CSA: AHI > 15, ≥ 50% CSA
- Eindpunt: Mortaliteit, levensreddende CV interventie, onverwachte zhs opname voor hartfalen.

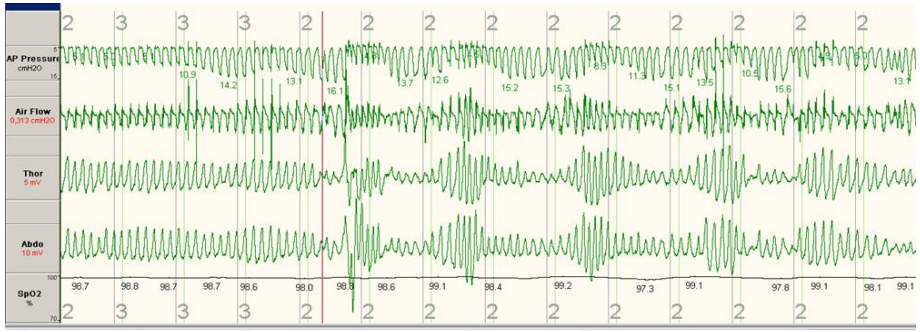
➢ Voortijdig gestopt bij 11% van doelpopulatie. N= 98

- PSG na minimaal 3 mnd: AHI daling ~50%, verbetering oxygenatie
- Geen verbetering overige eindpunten.

Redline S, et al. Ann AM Thorac Soc 2025

Adaptive Servo Ventilation (ASV)

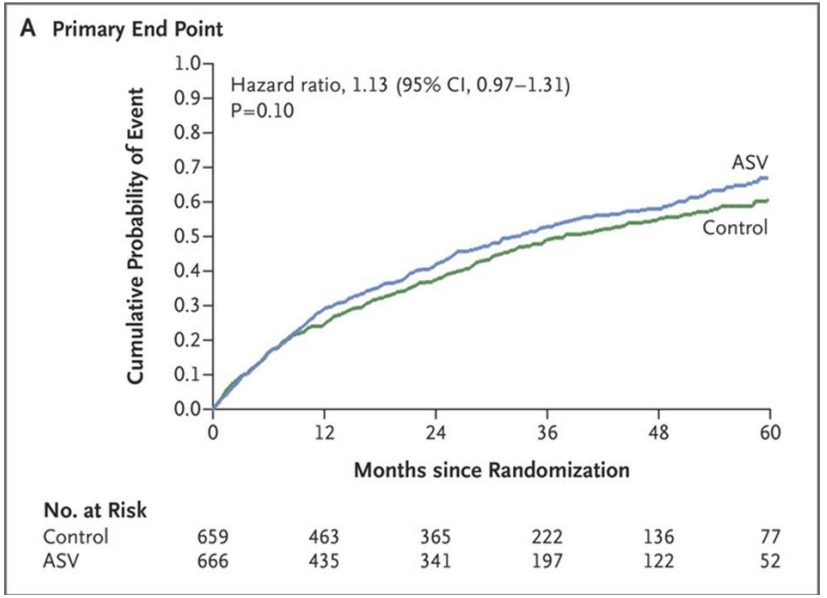




Oldenburg O, Circulation J 2012

SERVE-HF study

- Multicenter (91) RCT
- 1325 HF ptn met CSA
  - NYHA II – IV, LVEF $\leq$ 45%
  - CSA AHI $\geq$ 15/u
  - ASV/usual care vs usual care

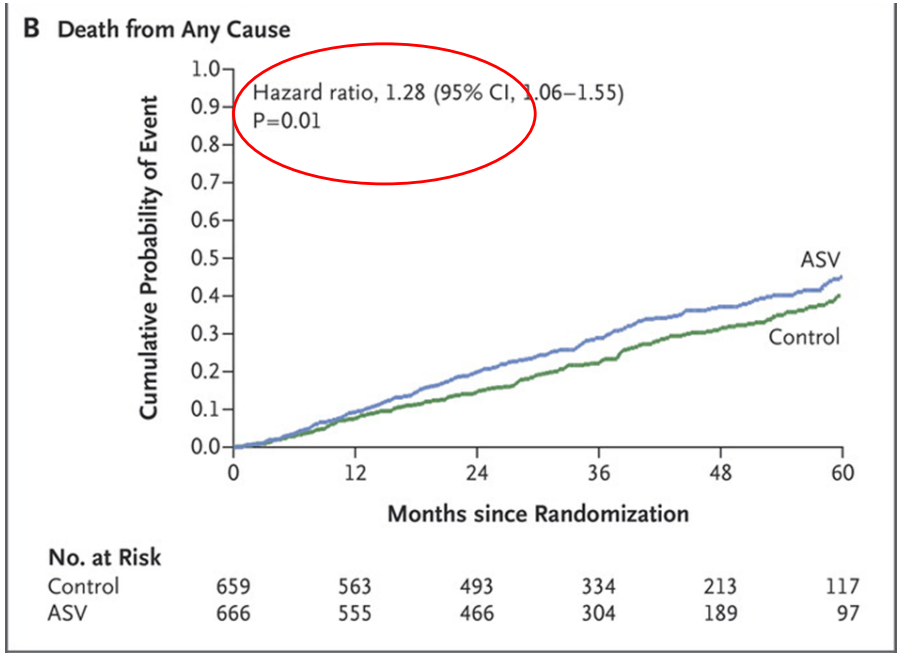


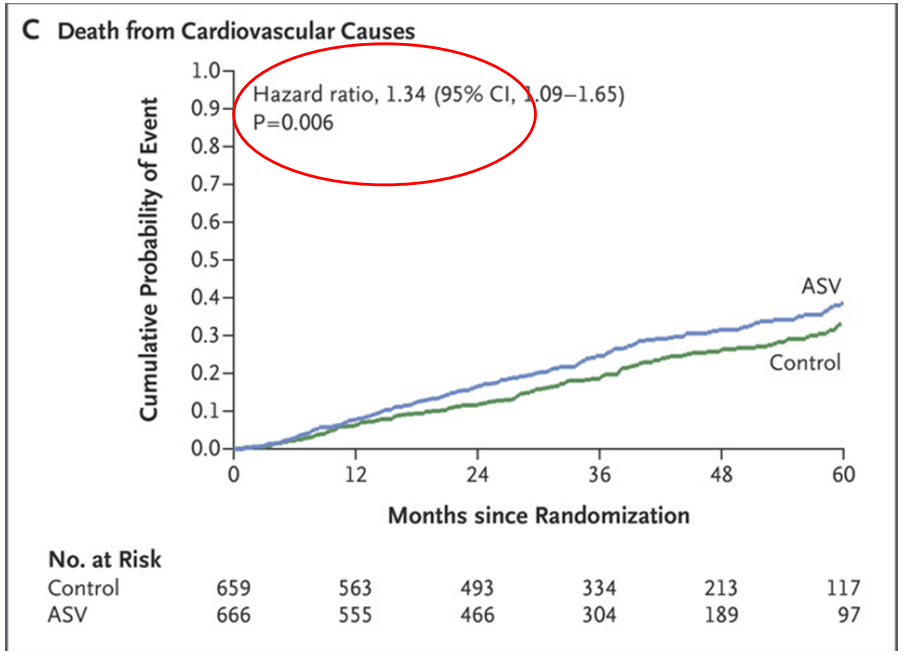
- Conclusion:

Intention to treat analysis: no difference in the primary endpoint (composite death from any cause, life saving cardiovascular intervention, or unplanned hospitalization for HF)

Cowie MR et al. N Engl J Med 2015

SERVE-HF study: secondary endpoints





Cowie MR et al. N Engl J Med 2015

AASM guideline update 2016

JCSM
Journal of Clinical Sleep Medicine

SPECIAL ARTICLES

Updated Adaptive Servo-Ventilation Recommendations for the 2012 AASM Guideline: "The Treatment of Central Sleep Apnea Syndromes in Adults: Practice Parameters with an Evidence-Based Literature Review and Meta-Analyses"

R. Nisha Aurora, MD, MHS[1]; Sabin R. Bista, MD[2]; Kenneth R. Casey, MD, MPH[3]; Susmita Chowdhuri, MD[4]; David A. Kristo, MD[5]; Jorge M. Mallea, MD[6]; Kannan Ramar, MD[7]; James A. Rowley, MD[8]; Rochelle S. Zak, MD[9]; Jonathan L. Heald, MA[10]

RECOMMENDATIONS

Adaptive Servo-Ventilation for the Treatment of Central Sleep Apnea Syndrome Related to Congestive Heart Failure

Recommendation 1: Adaptive servo-ventilation (ASV) targeted to normalize the apnea-hypopnea index (AHI) should not be used for the treatment of CSAS related to CHF in adults with an ejection fraction ≤ 45% and moderate or severe CSA predominant, sleep-disordered breathing. (STANDARD AGAINST)

"Pending publication ADVENT-HF trial.."

ADVENT-HF study

Adaptive servo-ventilation for sleep-disordered breathing in patients with heart failure with reduced ejection fraction (ADVENT-HF): a multicentre, multinational, parallel-group, open-label, phase 3 randomised controlled trial

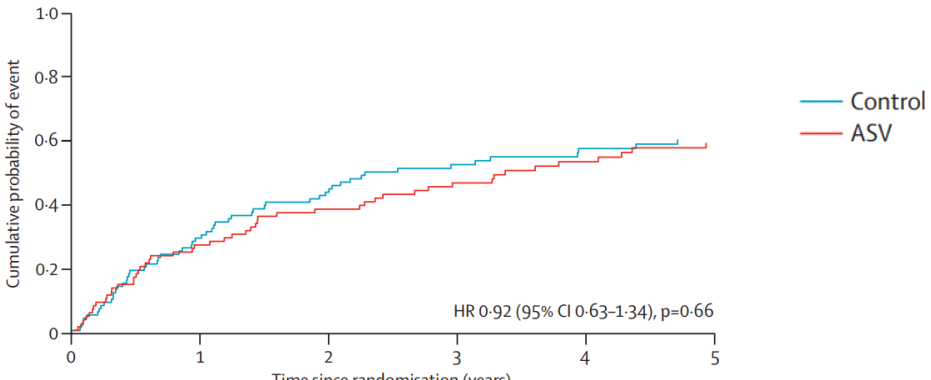
T Douglas Bradley, Alexander G Logan, Geraldo Lorenzi Filho, R John Kimoff, Joaquin Durán Cantolla, Michael Arzt, Stefania Redolfi, Gianfranco Parati, Takatoshi Kasai, Mark E Dunlap, Diego Delgado, Shoichiro Yatsu, Adriana Bertolami, Rodrigo Pedrosa, George Tomlinson, Jose M Marin Trigo, Claudio Tantucci, John S Floras, on behalf of the ADVENT-HF Investigators

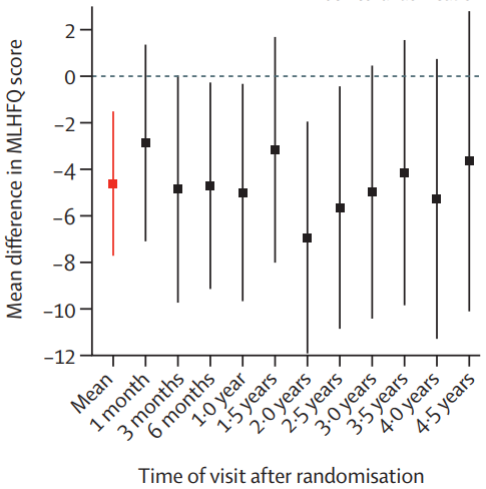
- N= 731, multicenter trial
  - LVEF $\leq$ 45%
  - AHI $\geq$ 15/u: 533 OSA and 198 CSA
- ASV/standard optimal treatment vs optimal treatment
- Primary Endpoint: cumulative incidence of the composite of all-cause mortality, first admission to hospital for CV reason, new onset atrial fibrillation or flutter, and delivery of an appropriate cardioverter-defibrillator shock
- Secondary endpoint: e.g. all-cause mortality, sleep structure, QOL, ESS

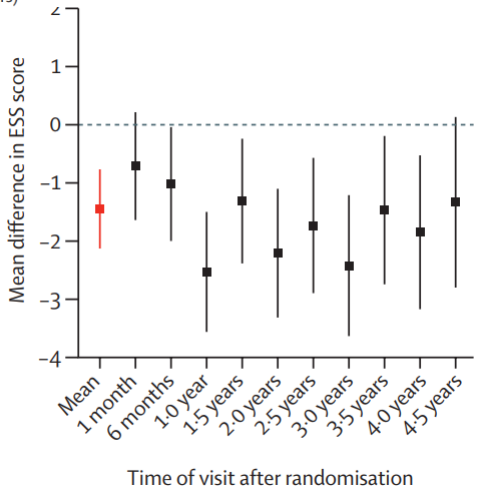
Bradley TD et al. Lancet Respir Med 2023

ADVENT-HF study: CSA ptn

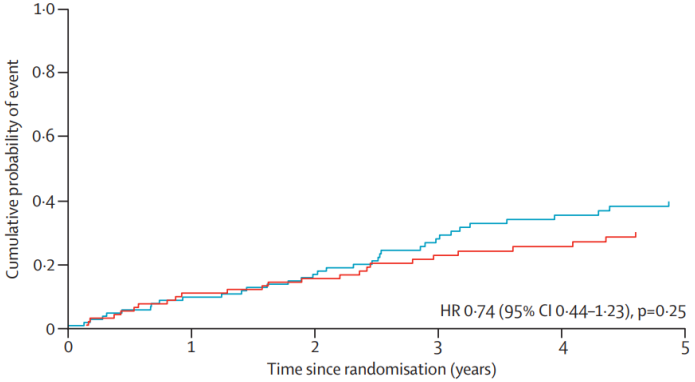
Cumulative probability of event curves for the primary endpoint







Cumulative probability of event curves for all-cause mortality



<u>Conclusion</u>

- 198/430 (46%) CSA pts included
- No effect on primary endpoint
- No effect on mortality
- Improvement QOL and ESS and NYHA

Too low power hence no definite conclusion regarding treatment of CSA in HFrEF and mortality

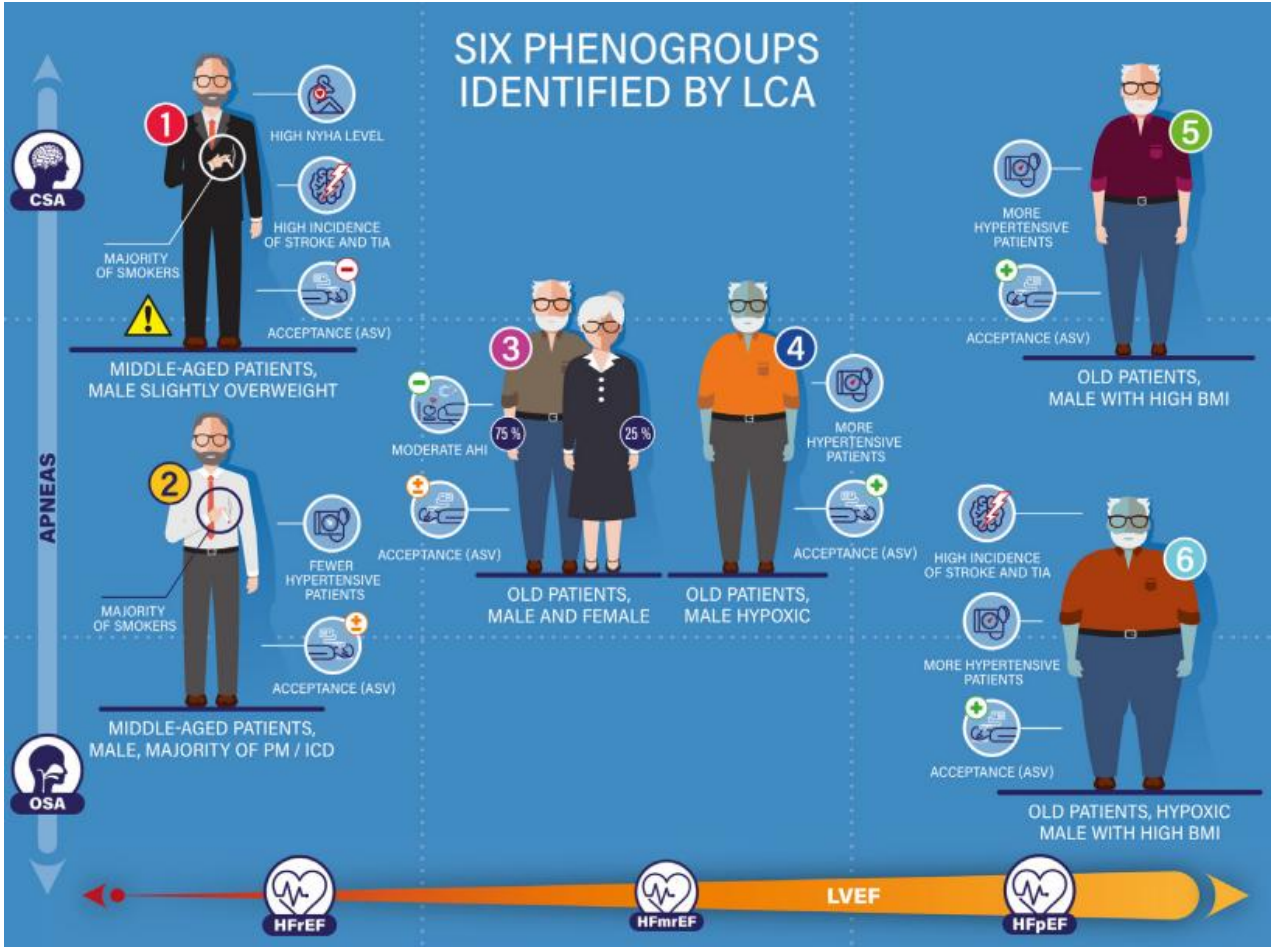
Bradley TD et al. Lancet Respir Med 2023

CSA fenotypen: FACE studie

- Multicenter prospective observational cohort trial
- 503 HF ptn met predominant CSA $\pm$ OSA component
- ASV vs controlegroep
- Inclusie 2009-2018
- Primaire eindpunt: tijd tot composite first event (all cause death, lifesaving CV intervention or unplanned hospitalisation for worsening of chronic HF.
- 6 onderscheidende clusters

Tamisier R, Thorax 2022
Tamisier R, Sleep Medicine 2023

CSA fenotypen: FACE studie



- Multicenter
- Prospectief cohort
- Inclusie 2009-2018
- 503 HF ptn met CSA
- ASV vs controle
- Primair eindpunt:

  Tijd tot composite first event:

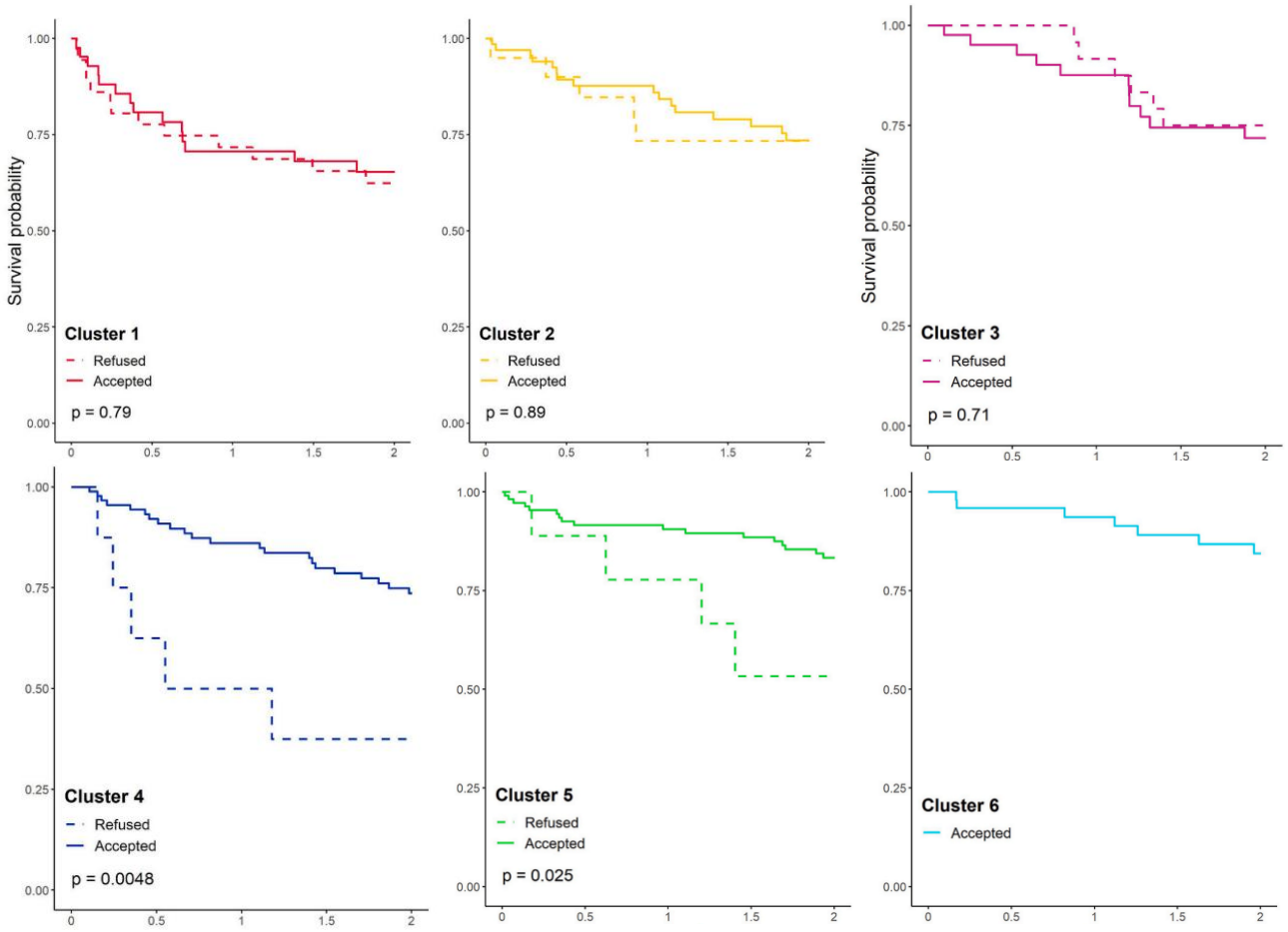
  All cause death

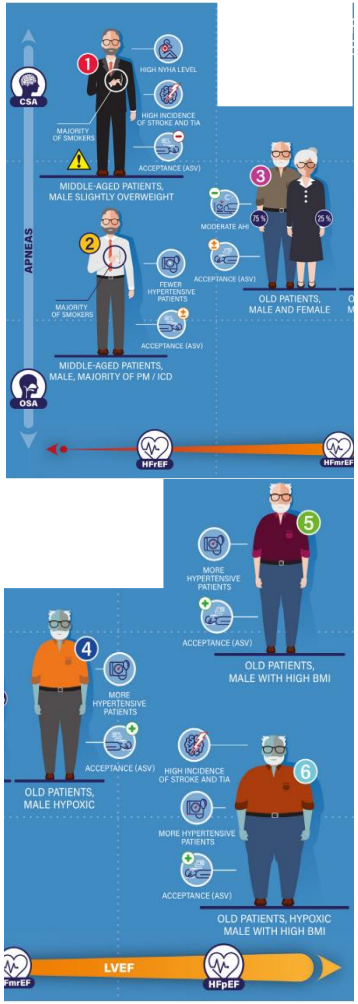
  Life saving CV intervention

  Unplanned hospitalisation for HF

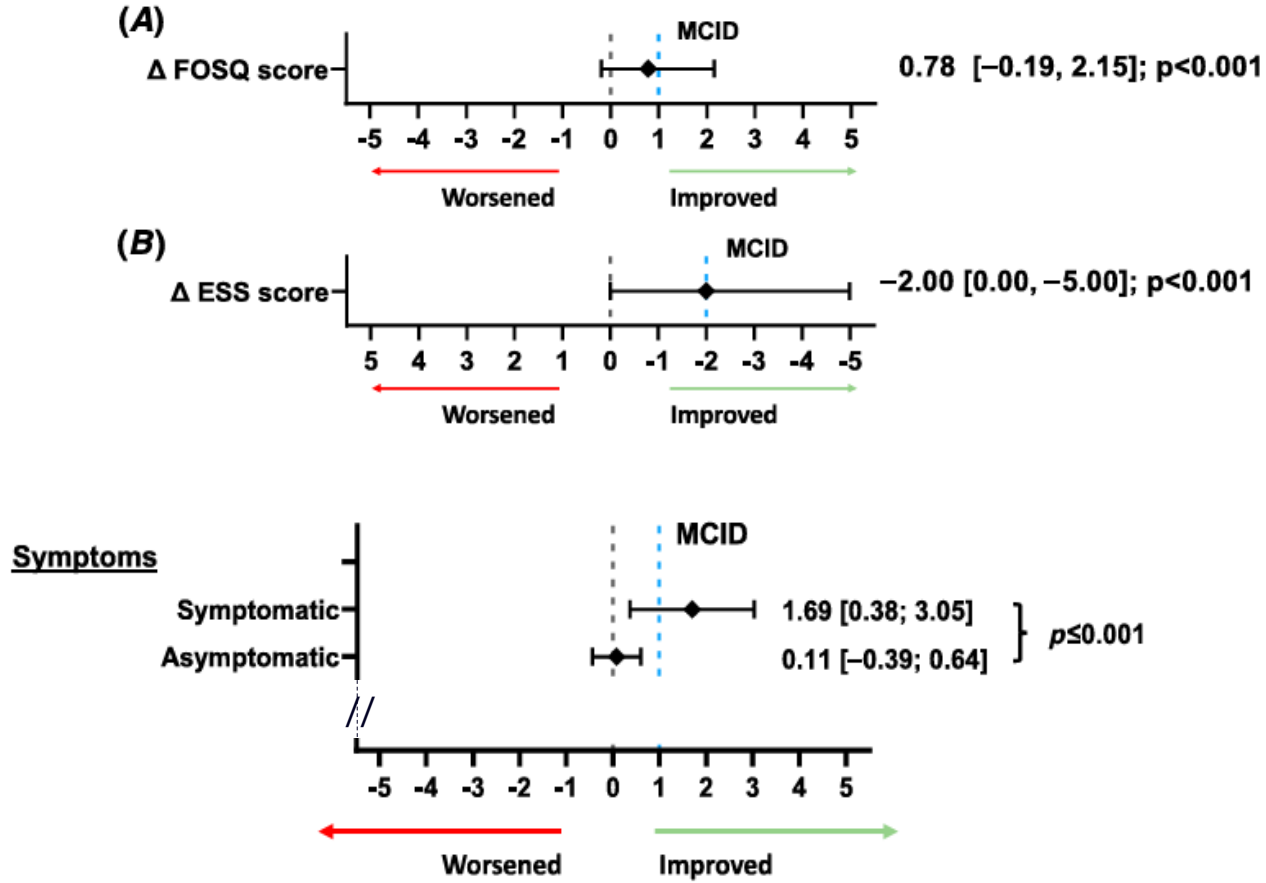
Tamisier R, Thorax 2022

FACE study: 2 jaar follow up





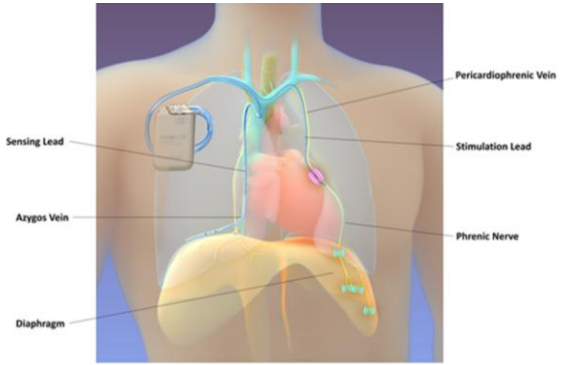
Read-ASV: effect op PROM

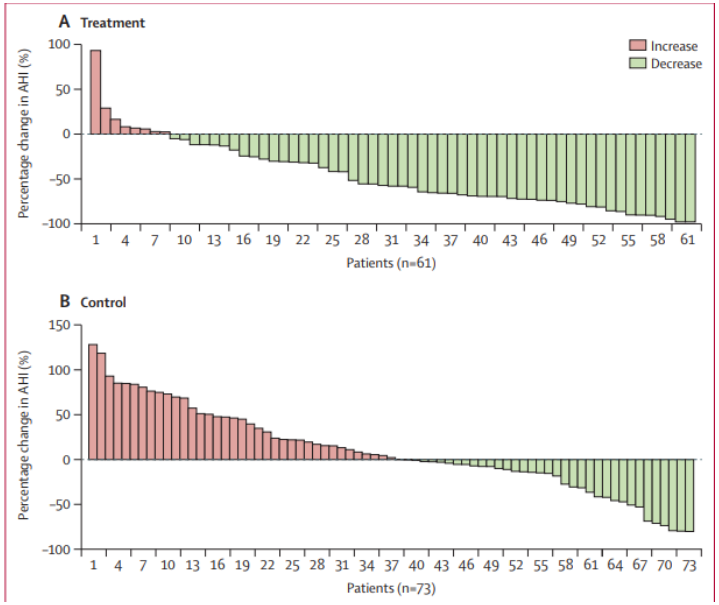


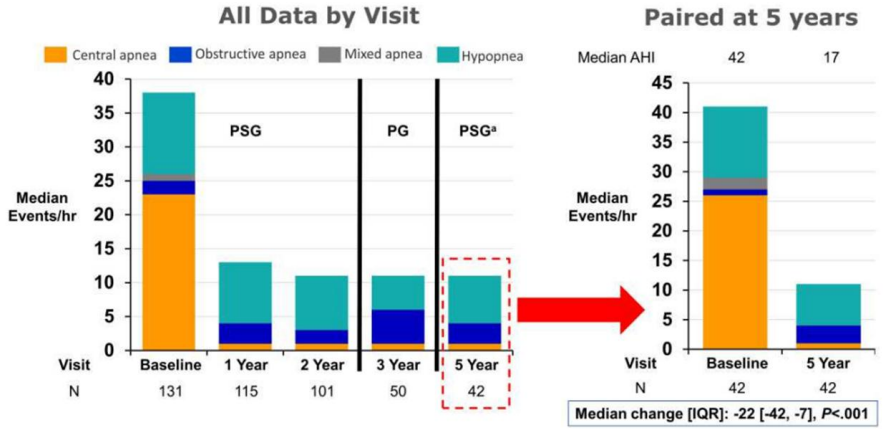
Arzt, Annals ATS 2024

N. Phrenicus stimulatie

- 151 CSA ptn, 31 centra
- AHI ≥ 20/u, OAI < 20% AHI







Costanzo MR. Lancet 2016 en Nature and science of sleep 2021

Medicatie

- Cardiale medicatie
- Stabilisatie van de ademhaling
  - 5 RCT (4 HF patienten)
  - N= 68 in totaal (!)
  - Acetazolamide, buspirone, theophylline, triazolam
  - Interventieperiode : 3 dagen- 1 week

Cochrane Library

Cochrane Database of Systematic Reviews

Pharmacological treatment for central sleep apnoea in adults (Review)

Authors' conclusions

There is insufficient evidence to support the use of pharmacological therapy in the treatment of CSA. Although small studies have reported positive effects of certain agents for CSA associated with heart failure in reducing the number of respiratory events during sleep, we were unable to assess whether this reduction may impact the quality of life of people with CSA, owing to scarce reporting of important clinical outcomes such as sleep quality or subjective impression of daytime sleepiness. Furthermore, the trials mostly had short-term follow-up. There is a need for high-quality trials that evaluate longer-term effects of pharmacological interventions.

Rocha A. Cochrane Database of Systematic Reviews 2023

Positie therapie in positioneel CSA

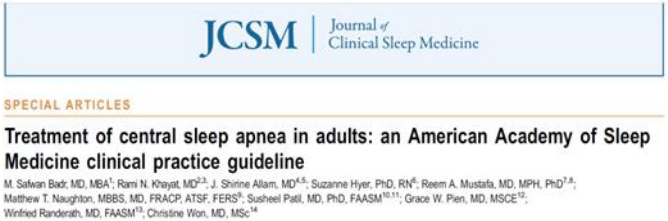
Table 2 Respiratory indices during baseline and after 1 month and 6 months of follow-up

	Baseline $N=16$	$T=1$ month $N=16$	$T=6$ months $N=13$	p value[a]	p value[b]
Total AHI, events/h	23.4 [12.9–31.2]	11.5 [7.2–24.5]	9.7 [3.4–27.6]	0.044*	0.075
Total AI, events/h	14.4 [8.6–29.7]	6.2 [1.5–17.9]	5.0 [0.7–23.7]	0.041*	0.087
Total central AI, events/h	9.4 [6.4–11.8]	2.5 [1.0–5.4]	0.9 [0.1–11.9]	0.008*	0.152
Oxygen Desaturation Index, events/h	16.3 [5.5–23.8]	6.9 [3.5–17.6]	7.1 [2.0–18.1]	0.041*	0.182
Supine AHI, events/h	59.8 [42.2–76.5]	62.2 [15.0–79.5]	20.2 [0.0–36.2]	0.807	0.013*
Non-supine AHI, events/h	7.3 [2.1–11.8]	7.6 [4.1–15.2]	5.2 [1.9–21.8]	0.163	0.124
Supine central AI, events/h	21.0 [12.9–36.9]	9.6 [0.5–22.0]	0.0 [0.0–18.1]	0.079	0.081
Non-supine central AI, events/h	1.4 [0.9–3.1]	1.2 [0.1–3.8]	0.7 [0.0–5.1]	0.363	0.937
Percentage supine sleep	37.6 [17.2–51.8]	6.7 [0.7–22.8]	6.8 [0.7–22.1]	<0.001*	0.001*
Total sleep time, h	6.7 [6.3–7.5]	6.9 [5.7–7.7]	7.0 [5.5–7.6]	0.717	0.600
Sleep efficiency, %	87.7 [72.3–92.4]	89.6 [79.6–94.0]	91.4 [78.1–95.0]	0.326	0.382
% REM	19.8 [16.1–23.1]	20.0 [12.7–22.4]	16.9 [11.8–26.4]	0.836	0.173
% Stage N1	5.7 [3.2–12.3]	7.4 [5.1–10.8]	6.9 [4.1–8.9]	0.918	0.917
% Stage N2	53.3 [45.0–58.0]	53.4 [44.9–59.7]	52.7 [49.7–60.3]	0.776	0.279
% Stage N3	19.3 [14.7–24.1]	20.7 [15.1–25.0]	21.3 [13.8–27.1]	0.717	0.917
Microarousal index, #/h	13.9 [3.1–35.9]	10.5 [5.4–16.5]	11.3 [5.6–15.9]	0.073	0.084
Positional change index, #/h	2.6 [1.9–3.7]	3.1 [1.8–5.7]	2.2 [1.2–4.8]	0.959	0.263
Minimal SpO_2 (%)	87.0 [84.3–88.0]	88.5 [86.3–91.0]	88.0 [86.5–90.5]	0.047*	0.062
Mean SpO_2	95.0 [93.5–96.0]	95.5 [95.0–96.0]	95.0 [94.0–96.0]	0.068	0.248
SpO2 < 90% (%TIB)	0.4 [0.03–2.03]	0.01 [0.00–0.28]	0.1 [0.0–0.3]	0.028*	0.171

N= 16 mannen
Positioneel CSA

Benoist LBL et al. Eur Arch Otorhinolaryngol. 2019

AASM Guideline CSA. Update 2025



In hartfalen patiënten:

- **Suggests CPAP over no CPAP**
- **Suggests ASV over no ASV**

  Remarks: Prior to initiation of adaptive servo-ventilation, patient-provider shared decision-making is recommended, and treatment decisions should be based on expectations of symptomatic or quality-of-life improvement. Treatment with adaptive servo-ventilation in patients with heart failure with reduced ejection fraction should be limited to centers with experience, along with close monitoring and follow-up.
- **Suggests low flow oxygen over no oxgen**
- **Suggests Acetazolamide over no Acetazolamide**
- **Suggests N. Phrenicus stimulatie over no N. Phrenicus stimulatie**.

  Remarks: Given that transvenous phrenic nerve stimulation requires an invasive procedure, is not universally accessible, and is associated with high costs,it may be more appropriate to consider other treatments first.
- **Suggests *against* BPAP without a backup rate**.

➢ GEEN 'Stepped Care' / volgorde in behandelingen aangegeven

Badr MS et al. J Clin Sleep Med. 2025

Federatie Medisch Specialisten
Kennisinstituut

De Nederlandse Richtlijn CSA komt er aan in 2026!

Take home message

- Hartfalen is de meest voorkomende oorzaak van CSA
- CSA is een onafhankelijke prognostische merker in hartfalen
- Fenotypen CSA in hartfalen
- Behandeling van CSA in hartfalen: doel is klachtenverbetering
- Meerdere behandelingsmogelijkheden.
  - Behandel de onderliggende oorzaak zo mogelijk
  - Stepped care behandeling, rekening houdend met onderliggende oorzaak
  - Afstemmen met pt/shared decision

➢ **Lees de Nederlands richtlijn CSA in 2026**