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Diagnosis and management of sleep apnea in stroke patients

Prof. Claudio L. Bassetti
Neurology Department
University Hospital, Bern
Switzerland

2016

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VIEWS & REVIEWS

Role of sleep-disordered breathing and sleep-wake disturbances for stroke and stroke recovery

OPEN

Dirk M. Hermann, MD
Claudio L. Bassetti, MD

Correspondence to
Prof. Dr. med. Hermann:
dirk.hermann@uk-essen.de
or Prof. Dr. med. Bassetti:
claudio.bassetti@insel.ch

ABSTRACT

Background: Sleep-disordered breathing (SDB) and sleep-wake disturbances (SWD) are highly prevalent in stroke patients. Recent studies suggest that they represent both a risk factor and a consequence of stroke and affect stroke recovery, outcome, and recurrence.

Methods: Review of literature.

Results: Several studies have proven SDB to represent an independent risk factor for stroke. Sleep studies in TIA and stroke patients are recommended in view of the very high prevalence (>50%) of SDB (Class IIb, level of evidence B). Treatment of obstructive SDB with continuous positive airway pressure is recommended given the strength of the increasing evidence in support of a positive effect on outcome (Class IIb, level of evidence B). Oxygen, biphasic positive airway pressure, and adaptive servoventilation may be considered in patients with central SDB. Recently, both reduced and increased sleep duration, as well as hypersomnia, insomnia, and restless legs syndrome (RLS), were also suggested to increase stroke risk. Mainly experimental studies found that SWD may in addition impair neuroplasticity processes and functional stroke recovery. Treatment of SWD with hypnotics and sedative antidepressants (insomnia), activating antidepressants or stimulants (hypersomnia), dopaminergic drugs (RLS), and clonazepam (parasomnias) are based on single case observations and should be used with caution.

Conclusions: SDB and SWD increase the risk of stroke in the general population and affect short- and long-term stroke recovery and outcome. Current knowledge supports the systematic implementation of clinical procedures for the diagnosis and treatment of poststroke SDB and SWD on stroke units. *Neurology*® 2016;87:1–10

2019

Sleep Medicine Reviews xxx (xxxx) xxx

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

EDITORIAL

Sleep and stroke: A bidirectional relationship with clinical implications

2019

EAN/ERS/ESO/ESRS statement on the impact of sleep disorders on risk and outcome of stroke

Claudio L.A. Bassetti*[2], Winfried Randerath*[1], Luca Vignatelli[4], Anne-Kathrin Brill[5], Maria R. Bonsignore[6], Ludger Grote[7], Poul Jennum[8], Didier Leys[9], Jens Minnerup[10], Lino Nobili[11], Thomy Tonia[12], Rebecca Morgan[13], Walter T. McNicholas[16], Joel Kerry[14], Luigi Ferini-Strambi**[3], Vasileios Papavasileiou**[15]

*co-shared first authorship ** co-shared senior authorship

Eur J Neurol (in press)
Eur Resp J (in press)

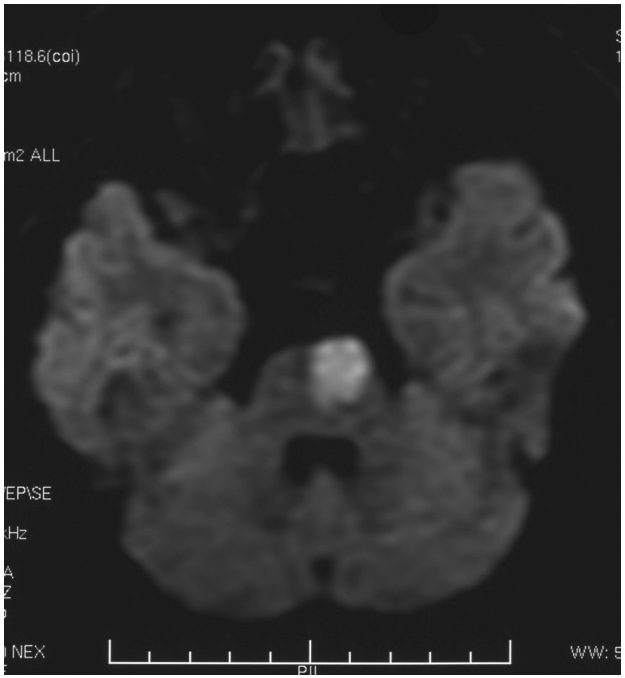
16 experts, 8 countries
neurology, pulmonology
stroke, methodology

Vignette-Question
Introduction
Frequency of SDB in stroke pts
Consequences of SDB in stroke pts
Diagnostic approach
Treatment
Vignette-Answer
Conclusions

V.C., 70y male

History

acute weakness, slurred speech
PA: diabetes, hypertension, obesity
no excessive daytime sleepiness



Status

dysarthria, hemiparesis, NIH=11
BMI=29

Work-Up

Blood tests: dyslipidemia, HbA1c=6.5
Echocardiography, 24h ECG, doppler: normal

V.C., 70y male

The following statement is correct:

A. A sleep disordered breathing (SDB) is probable
B. The absence of sleepiness makes a SDB unlikely
C. The diagnosis of SDB in the stroke unit is difficult
D. The treatment of SDB in acute stroke patients is usually not possible and has no long-term effects

Vignette-Question

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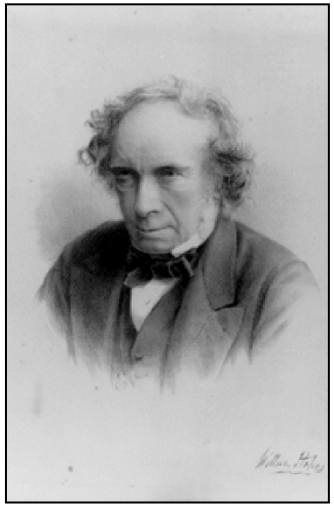
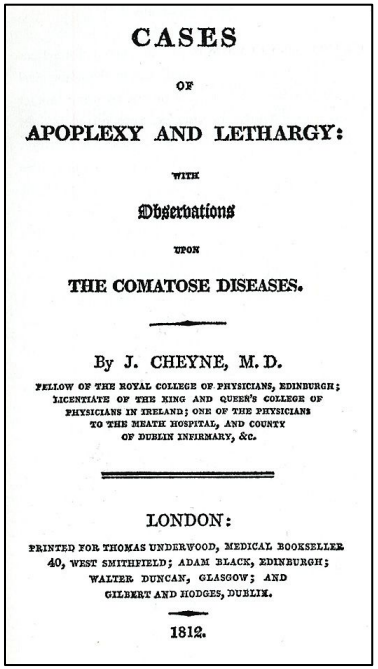
Cheyne-Stokes breathing (CSB)





CASES

OF

APOPLEXY AND LETHARGY:

WITH

Observations

UPON

THE COMATOSE DISEASES.

By J. CHEYNE, M. D.

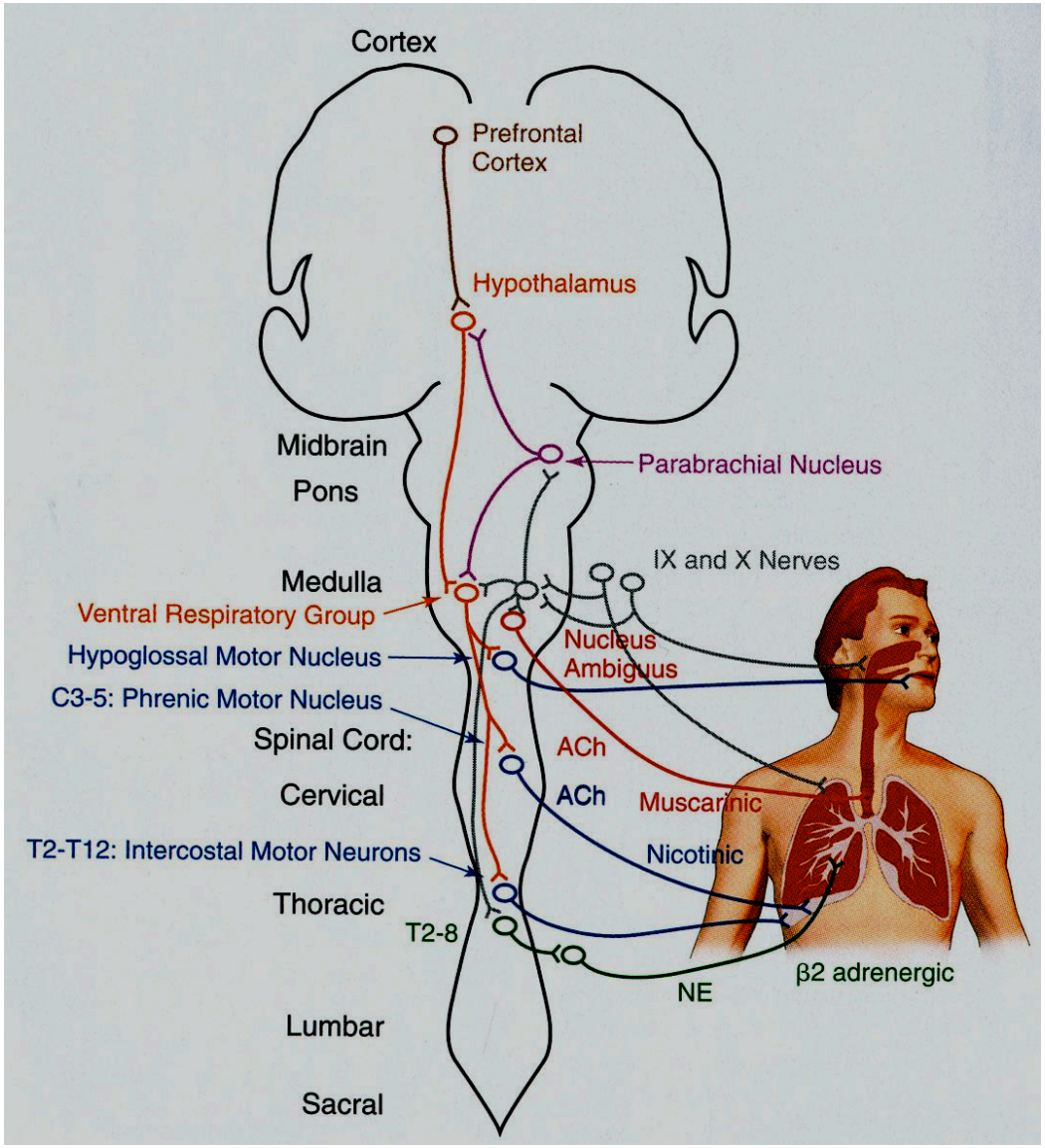
FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS, EDINBURGH; LICENTIATE OF THE KING AND QUEEN'S COLLEGE OF PHYSICIANS IN IRELAND; ONE OF THE PHYSICIANS TO THE MEATH HOSPITAL, AND COUNTY OF DUBLIN INFIRMARY, &c.

LONDON:

PRINTED FOR THOMAS UNDERWOOD, MEDICAL BOOKSELLER 40, WEST SMITHFIELD; ADAM BLACK, EDINBURGH; WALTER DUNCAN, GLASGOW; AND GILBERT AND HODGES, DUBLIN.

1812.

"On the 10th of April he was found in bed, speechless, and hemiplegiac. . . . The only peculiarity in the last period of his illness, which lasted eight or nine days, was in the state of the respiration. For several days, his breathing was irregular; it would cease for a quarter of a minute, then it would become perceptible, though very low, then by degrees it became heaving and quick, and then it would gradually cease again. This revolution in the state of his



Plum and Posner, The diagnosis of Stupor and Coma

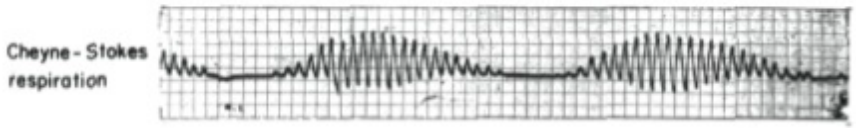
Types of SDB in stroke

- Obstructive sleep apnea
- Central sleep apnea (periodic breathing, Cheyne-Stokes)
- Mixed apneas

<u>Modulators</u>

- Sleep stage
- Position
- Interval after stroke

Cheyne-Stokes breathing after supratentorial stroke



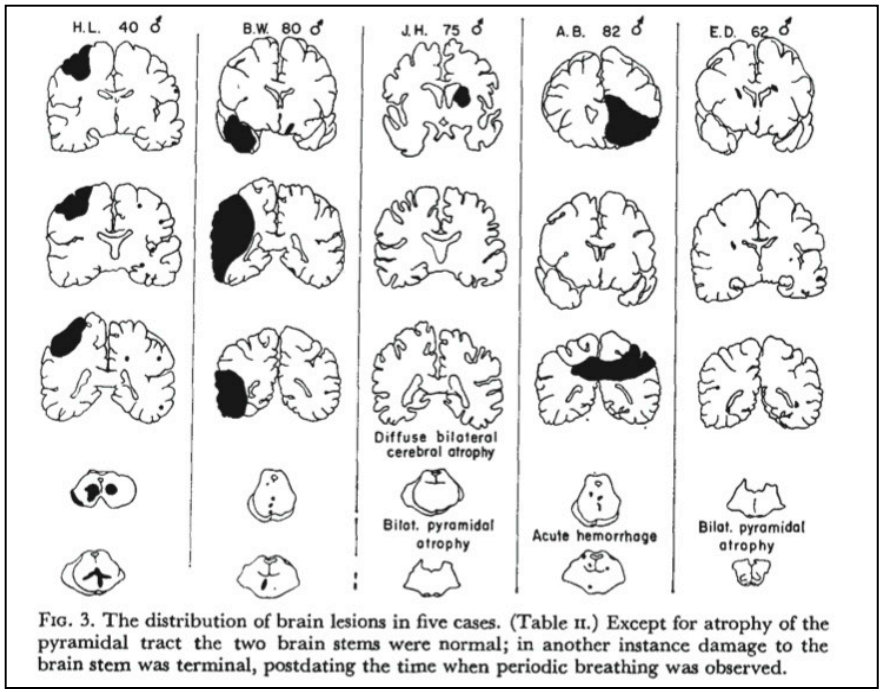


FIG. 3. The distribution of brain lesions in five cases. (Table II.) Except for atrophy of the pyramidal tract the two brain stems were normal; in another instance damage to the brain stem was terminal, postdating the time when periodic breathing was observed.

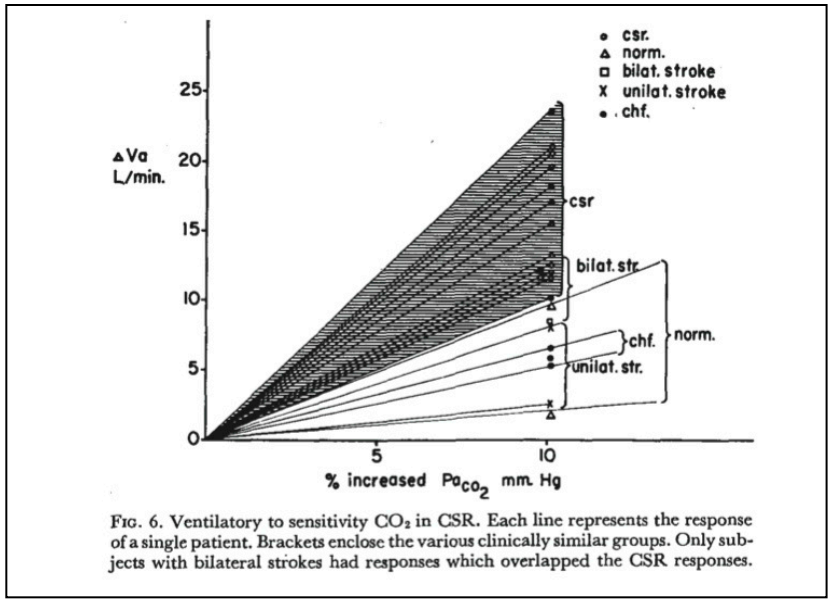


FIG. 6. Ventilatory to sensitivity CO_2 in CSR. Each line represents the response of a single patient. Brackets enclose the various clinically similar groups. Only subjects with bilateral strokes had responses which overlapped the CSR responses.

Brown and Plum, Am J Med 1961

SDB and brainstem stroke

n=355, 13 days after stroke , ApneaLink Plus™

Table 2
Sleep-disordered breathing indices, presented as medians and interquartile ranges, in ischemic stroke subjects ($n = 355$) with and without brainstem infarction.

	Apnea–hypopnea index	Obstructive apnea index	Central apnea index	Hypopnea index
Brainstem infarction ($n = 38$)	20 (11, 38)	3 (1, 11)	1 (0, 3)	11 (6, 15)
No brainstem infarction ($n = 317$)	13 (6, 26)	3 (1, 10)	0 (0, 0)	6 (2,12)
p value	0.007	0.622	0.04	0.002
Midbrain infarction only ($n = 7$)	22 (19, 44)	6 (2, 14)	2 (0, 4)	17 (9, 22)
Pontine infarction only ($n = 27$)	16 (11, 35)	2 (1, 10)	1 (0, 3)	10 (6, 14)
Pontine and medullary infarction ($n = 3$)	37 (24, 38)	7 (4, 15)	1 (1, 4)	15 (13, 19)

Brown, Sleep Med 2014

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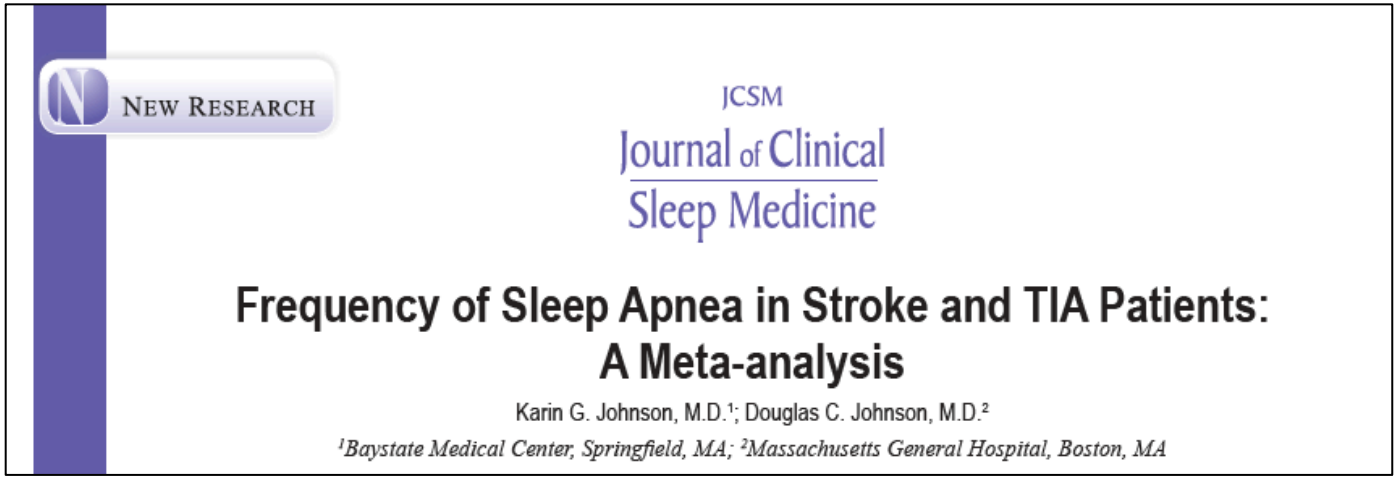


Johnson, J Clin Sleep Med 2010

29 studies (until 12.2008)
2343 pts

AHI> 10 in 63% (23 studies)
AHI>30 in 29% (10 studies)

Published Ahead of Print on January 11, 2019 as 10.1212/WNL.0000000000006904

ARTICLE

Prevalence of sleep-disordered breathing after stroke and TIA

A meta-analysis

Andrea Seiler, MD, Millene Camilo, MD, PhD, Lyudmila Korostovtseva, MD, PhD, Alan G. Haynes, PhD, Anne-Kathrin Brill, MD, Thomas Horvath, MD, Matthias Egger, MD,* and Claudio L. Bassetti, MD*

Correspondence
Prof. Bassetti
claudio.bassetti@insel.ch

Neurology® 2019;92:1-7. doi:10.1212/WNL.0000000000006904

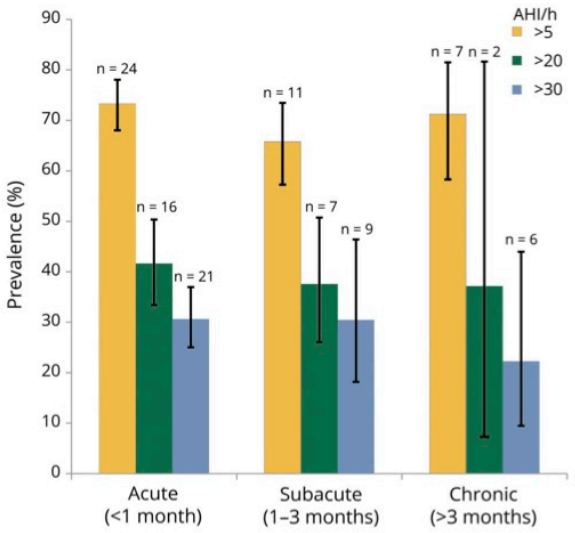
2019

Seiler, Neurology 2019

89 studies (until 4.2017)
7096 pts

AHI> 5 in 71%
AHI>30 in 30%

Figure 2 Prevalence of AHI >5/h, >20/h, and >30/h for the acute, subacute, and chronic phase after stroke or TIA



Prevalence in percentage of all included patients across the studies with 95% confidence interval. AHI = apnea-hypopnea index; n = number of studies available.

SAS-CARE Study

2019

Ott (submitted)

Sleep-disordered breathing in acute ischemic stroke and transient ischemic attack: effects on short- and long-term outcome and efficacy of treatment with continuous positive airways pressure – rationale and design of the SAS CARE study

Carlo W. Cereda[1], Liliane Petrini[1], Andrea Azzola[2], Alfonso Ciccone[3], Urs Fischer[4], Augusto Gallino[5], Sandor Györik[5], Matthias Gugger[6], Johannes Mattis[4], Lena Lavie[7], Costanzo Limoni[1], Lino Nobili[3], Mauro Manconi[1], Sebastian Ott[6], Marco Pons[2], and Claudio L. Bassetti[1,5]*

Int J Stroke 2012

- Full PSG within 1 week
- AASM 2012 criteria

- 168 consecutive stroke pts
- 74% stroke, 26% TIA
- male 72%, mean age 61±9
- NIHSS: 4±5 (0-40)

- 50% AHI>15
- 30% AHI>30

- obstructive (84%)
- central (13%)

bad outcome at 3 months

- high NIHSS/AHI

SDB improves after acute stroke and TIA

stable phase: after 3 months

TIME COURSE OF SLEEP RESPIRATORY DISTURBANCES: DIFFERENCES BETWEEN THE ACUTE AND STABLE PHASE IN A SUBGROUP OF 86 PATIENTS, CONSIDERING DIFFERENT STROKE SUBTYPES

	Transient Ischemic Attack Phase		Ischemic Stroke Phase		Hemorrhagic Stroke Phase	
	Acute	Stable	Acute	Stable	Acute	Stable
Patients, n	23	23	59	59	4	4
BMI, kg/m^2	27.6 ± 5	27.4 ± 4.3	26.8 ± 4.1	26.5 ± 3.8	24.7 ± 3.6	24.8 ± 2
AHI	22.3 ± 16.4	12.9 ± 12.1*	21.8 ± 17.8	17.7 ± 14.1†	30 ± 17.1	26.8 ± 14
OAI	8.5 ± 12.2	5.7 ± 9.3	3.4 ± 6.6	4.1 ± 6.4	1.9 ± 3.3	5.5 ± 7.9
CAI	3.6 ± 6.5	1.04 ± 3.1*	5.9 ± 9.9	3.3 ± 7.7†	23.6 ± 16.3	15.2 ± 13
AHI						
> 10	7/23	10/23	40/59	38/59	3/4	3/4
> 30	3/23	4/23	18/59	11/59	3/4	3/4
CSB, n	5/23	0/23	10/59	6/59	2/4	0/4
CT_{90}, %	11.2 ± 16.3	8.2 ± 15.2	9.6 ± 20	5.4 ± 16.6†	11.6 ± 7.5	3.5 ± 3.9

For definition of abbreviations, *see* Table 1.
* Comparisons with baseline made with nonparametric tests.
† Comparisons with baseline made with parametric tests.

Parra, AJRCCM 2000

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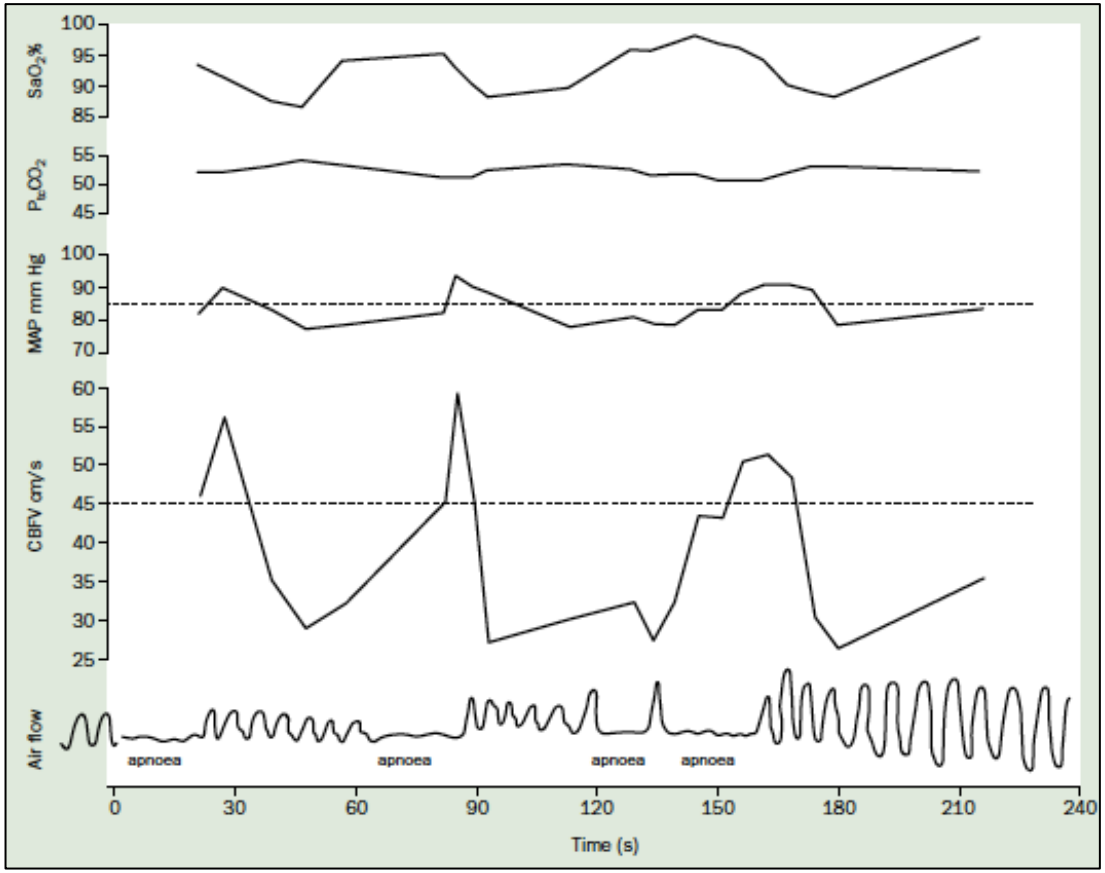
Detrimental effects of SDB on stroke (short-term)

- Recurrent hypoxemia
- Increased/variable blood pressure
- Increased cardiac arrhythmias (?)
- Cerebral hypoperfusion
- Longer hospitalization (costs)

- Stroke progression?
- Short-term outcome?

Detrimental acute effects of SDB



oxygen desaturations

blood pressure swings

cerebral blood flow velocity swings

respiratory events

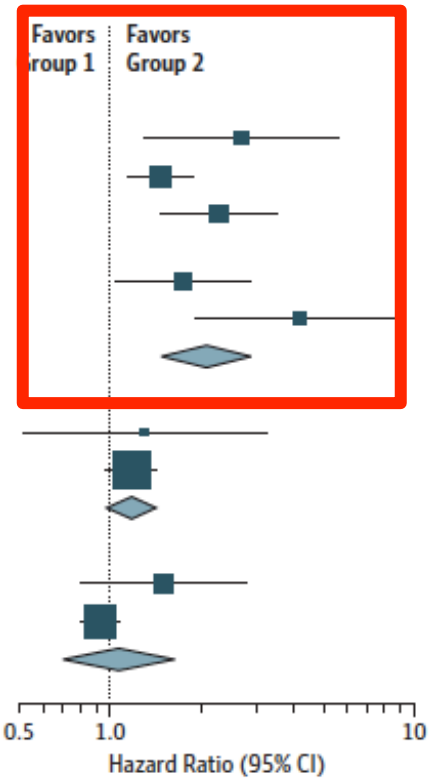
Yaggi and Mohsenin, Lancet Neurol 2004

Detrimental effects of SDB on stroke (longterm)

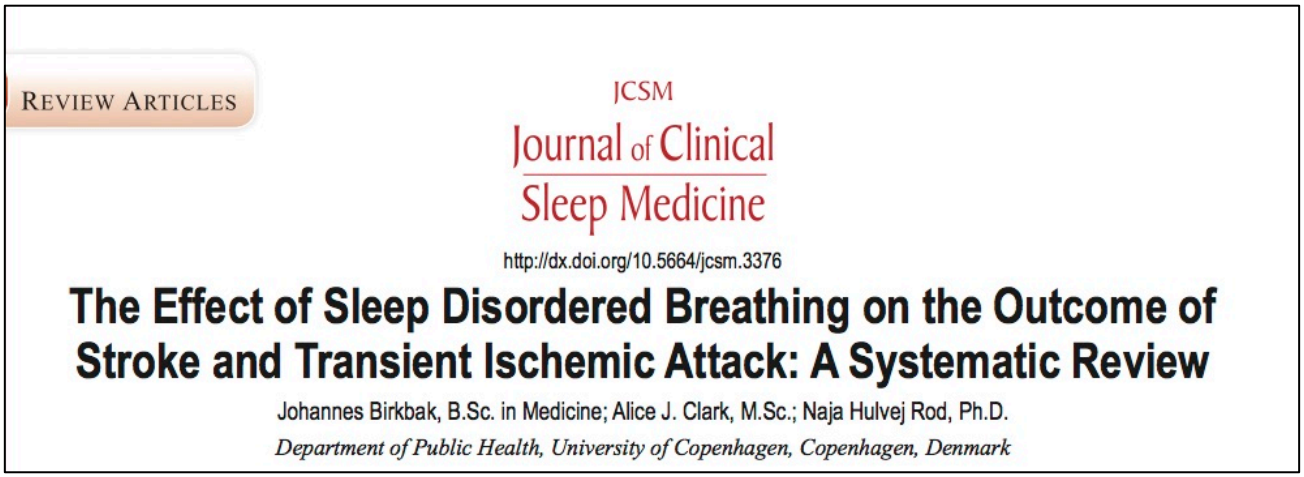
- Increased mortality
- Increased cardiovascular morbidity
- Poorer stroke outcome

Detrimental long-term effects of SDB

Source	No. of Deaths/ Total No. (%) Group 1	No. of Deaths/ Total No. (%) Group 2	Follow-up, y	Apnea-Hypopnea Index Comparison, Group 1 vs Group 2	Hazard Ratio (95% CI)	Weight, %
Severe OSA						
Young et al,[150] 2008	12/63 (19.0)	46/1157 (4.0)	13.8	≥30 vs <5	2.70 (1.29-5.65)	13.47
Punjabi et al,[151] 2009	86/341 (25.2)	477/3429 (13.9)	8.2	≥30 vs <5	1.46 (1.14-1.86)	31.27
Gooneratne et al,[147] 2011	35/42 (83.3)	59/119 (49.6)	13.8	≥20 and EDS vs <20 and no EDS	2.28 (1.46-3.57)	22.66
Ensrud et al,[144] 2012	25/209 (12.0)	155/2296 (6.8)	3.4	≥30 vs <30	1.74 (1.04-2.90)	20.22
Marshall et al,[153] 2014	10/18 (55.6)	54/294 (18.4)	20	≥15 vs <5	4.20 (1.91-9.24)	12.38
Subtotal (I^2 = 57.8%, P = .05)					2.07 (1.48-2.91)	100.0
Moderate OSA						
Young et al,[150] 2008	6/82 (7.3)	46/1157 (4.0)	13.8	15 to <30 vs <5	1.30 (0.51-3.29)	4.04
Punjabi et al,[151] 2009	165/727 (22.7)	477/3429 (13.9)	8.2	15 to <30 vs <5	1.17 (0.97-1.42)	95.96
Subtotal (I^2 = 0.0%, P = .83)					1.17 (0.97-1.42)	100.0
Mild OSA						
Young et al,[150] 2008	16/220 (7.3)	46/1157 (4.0)	13.8	5 to <15 vs <5	1.50 (0.80-2.81)	28.94
Punjabi et al,[151] 2009	319/1797 (17.8)	477/3429 (13.9)	8.2	5 to <15 vs <5	0.93 (0.80-1.08)	71.06
Subtotal (I^2 = 52.7%, P = .15)					1.07 (0.70-1.63)	100.0



Jonas, JAMA 2017


REVIEW ARTICLES

JCSM
Journal of Clinical Sleep Medicine

http://dx.doi.org/10.5664/jcsm.3376

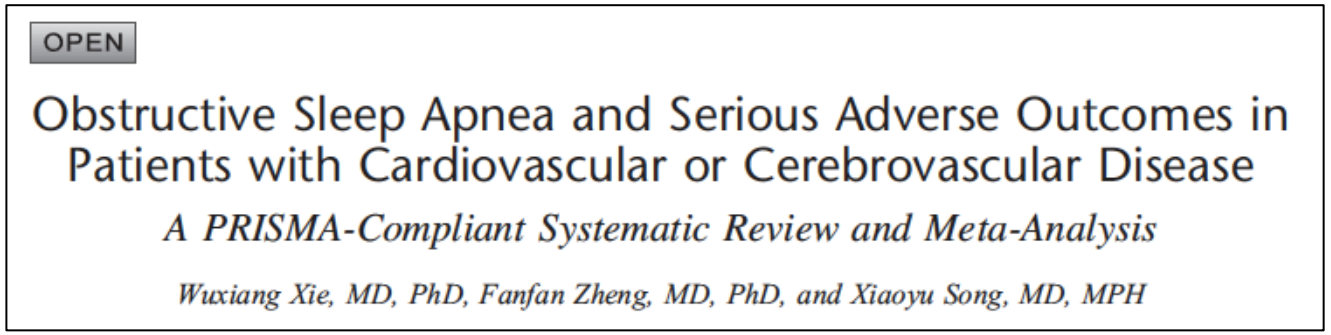
The Effect of Sleep Disordered Breathing on the Outcome of Stroke and Transient Ischemic Attack: A Systematic Review

Johannes Birkbak, B.Sc. in Medicine; Alice J. Clark, M.Sc.; Naja Hulvej Rod, Ph.D.

Department of Public Health, University of Copenhagen, Copenhagen, Denmark

2014

Birkbak, J Clin Sleep Med 2014


OPEN

Obstructive Sleep Apnea and Serious Adverse Outcomes in Patients with Cardiovascular or Cerebrovascular Disease

A PRISMA-Compliant Systematic Review and Meta-Analysis

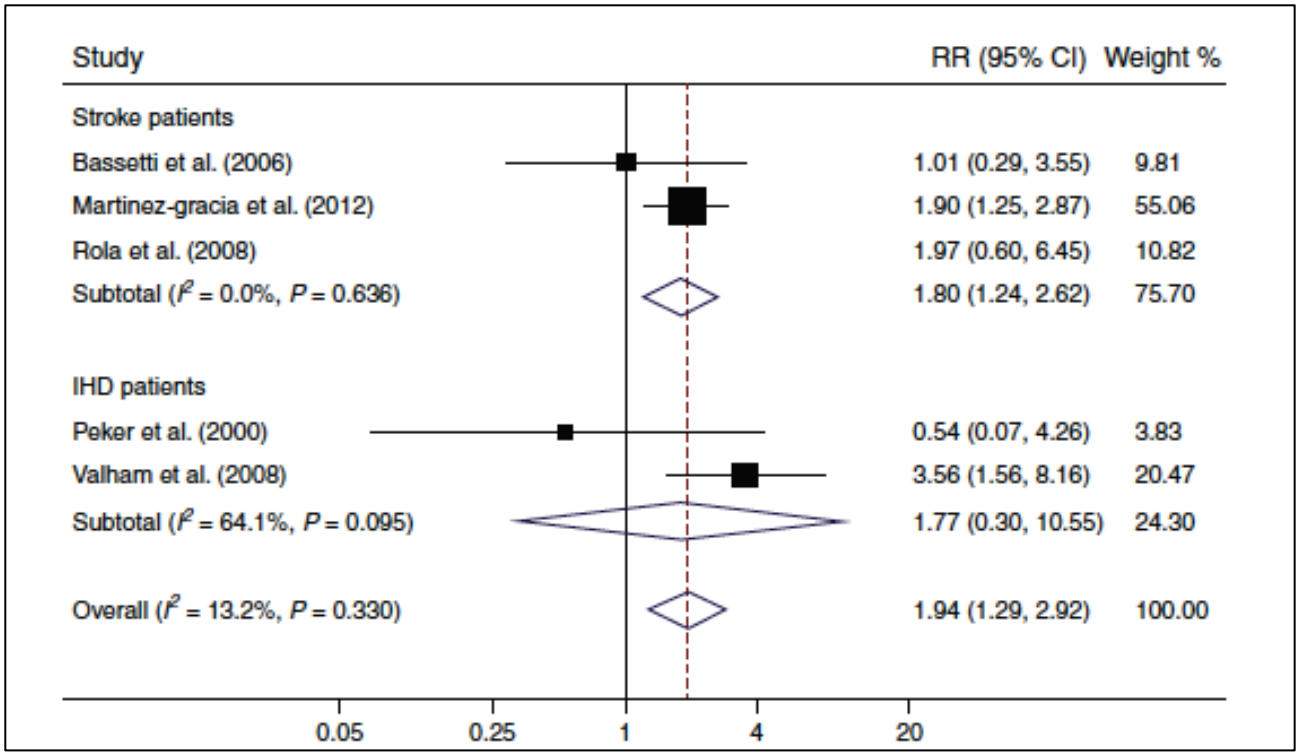
Wuxiang Xie, MD, PhD, Fanfan Zheng, MD, PhD, and Xiaoyu Song, MD, MPH

2014

Xie, Medicine 2014

Stroke risk in OSA pts after stroke/IHD
(ischemic heart disease)

hospital-based cohort studies, OR 1.9 (95%, CI 1.3-2.9)



Xie, Medicine 2014

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Predictors of obstructive SDB

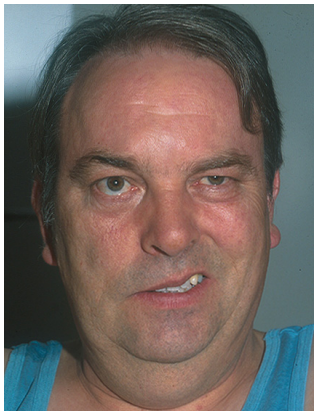

TABLE 6. Independent Predictors of AHI

	Wald's Statistic	*P* Value	Odds Ratio
Age	14.722	0.000	1.069
Diabetes	6.056	0.014	4.269
Nighttime onset of stroke*	4.367	0.037	2.641

Logistic regression analysis, dependent variable: AHI.
Nagelkerke $r^2=0.295$.
*Onset of stroke between 9:01 PM and 6.00 AM, 25%; between 6:01 AM and 9:00 PM, 75%.

Bassetti, Milanova, Gugger, Stroke 2006

Night-time and wake-up strokes and SDB

TABLE 6. Independent Predictors of AHI

	Wald's Statistic	*P* Value	Odds Ratio
Age	14.722	0.000	1.069
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Bassetti, Stroke 2006

Table 4 Clinical differences between patients with and without SRSO

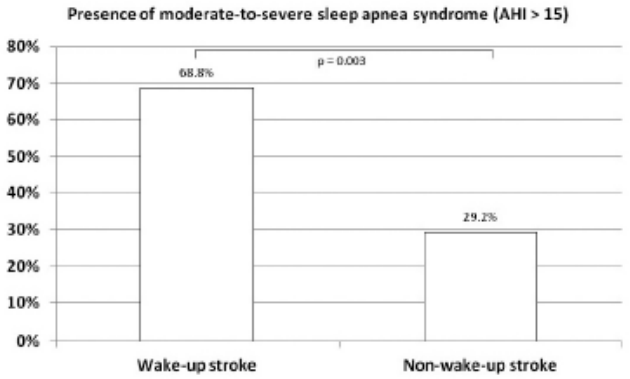
Characteristic	With SRSO	Without SRSO	*p* value
Patient (*n*)	17	57	
Age (years)	68.8±10.2	62.4±8.9	0.01
Sex (M:F)	11:6	28:29	0.26
AHI (no./h)	25.4±18.1	12.5±11.1	0.001[a]
AHI >10 (%)	82.4	45.6	0.01[a]
BMI (kg/m^2)	24.6±2.7	24.6±3.4	0.65[a]
HTN (%)	70.5	50.8	0.14[a]
DM (%)	35.2	29.8	0.71[a]
Smoking (%)	29.4	28.0	0.38[a]
Alcohol (%)	52.9	26.3	0.02[a]

[a] *p* value after adjustment of age

SRSO sleep-related stroke onset, *AHI* apnea–hypopnea index, *BMI* body mass index, *HTN* hypertension, *DM* diabetes mellitus

Joo, Sleep Breath 2010

Figure 3—Presence of moderate-to-severe sleep apnea syndrome in patients with wake-up stroke and non-wake-up stroke (68.8% vs. 29.2%, p = 0.003).



Siarnik, J Clin Sleep Med 2016

Nocturnal Desaturation in the Stroke Unit Is Associated With Wake-Up Ischemic Stroke

Tae Jung Kim, MD; Sang-Bae Ko, MD, PhD; Han-Gil Jeong, MD; Ji Sung Lee, PhD; Chi Kyung Kim, MD, PhD; Yerim Kim, MD; Kiwoong Nam, MD; Heejung Mo, MD; Sang Joon An, MD; Huimahn Alex Choi, MD; Byung-Woo Yoon, MD, PhD

Predictors of central SDB

Postacute phase
left ventricular ejection fraction

TABLE 3. MULTIVARIATE ODDS RATIOS FOR CENTRAL SLEEP APNEA

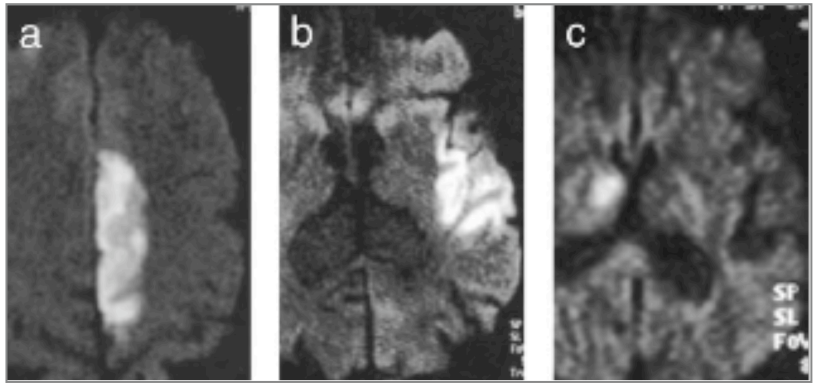
Variables	Odds Ratio	p Value	95% Confidence Interval	
			Lower	Upper
Age	2.1	0.399	0.4	12.2
Sex	0.3	0.133	0.1	1.4
Atrial fibrillation	0.4	0.278	0.1	2.3
Ptc_{CO_2}	0.8	0.017	0.7	0.9
LVEF ≤ 40%	8.5	0.040	1.1	66.1

Definition of abbreviations: LVEF = left ventricular ejection fraction; Ptc_{CO_2} = transcutaneous Pco_2.

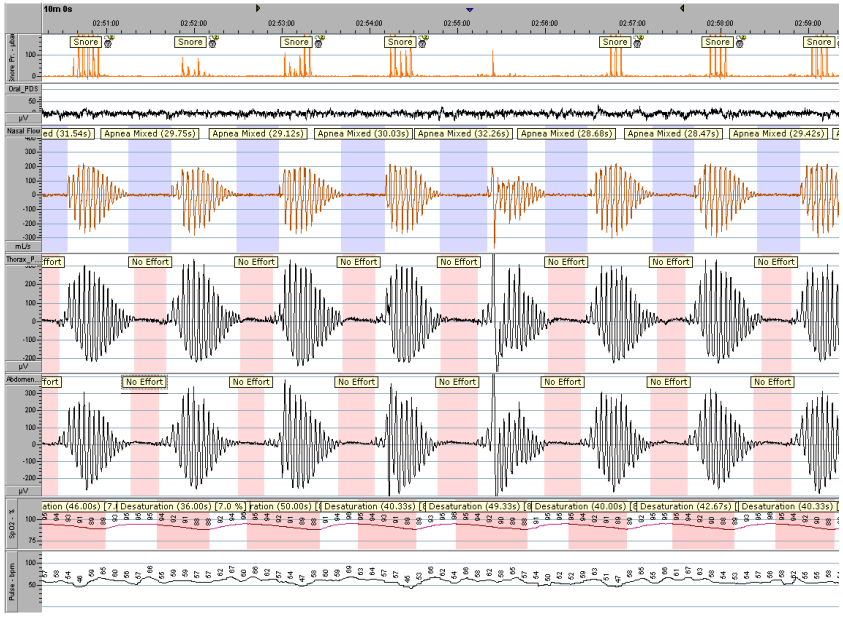
Nopmaneejumruslers, AJRCCM 2005

Acute phase
stroke topography

n=77
45±26 hours after stroke:
AHI>10 in 53%
CSA >10% of time in 39%



Hermann, Stroke 2007, Siccoli, J Neurol 2008



48-year-old man moderate hemispheric stroke (NIHSS=12)

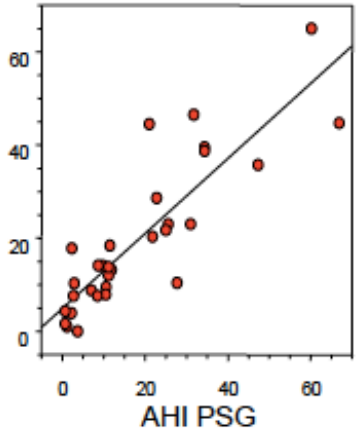
sleep study at Day 3
no EDS

Apnea-Hypopnea-Index=44
80% central
min SaO_2=86%

SDB and stroke: Diagnosis

- Excessive sleepiness is uncommon in stroke pts with SDB
- Predictors: snoring, age/gender, obesity, night-time onset
- Portable devices*: accurate/validated tools for screening
- Severity often improves in the first few weeks

*ResMed AutoSet®
ApneaLink Plus™



Bassetti, Stroke 1996; Reeves, Sleep Med 2014; Brown, Sleep Med 2014

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Articles
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THELANCETRM-D-16-00146R2
S2213-2600(16)30075-3
Embargo: June 14, 2016 [23:30] BST

The NoSAS score for screening of sleep-disordered breathing: a derivation and validation study

Helena Marti-Soler, Camila Hirotsu, Pedro Marques-Vidal, Peter Vollenweider, Gérard Waeber, Martin Preisig, Mehdi Tafti, Sergio Brasil Tufik, Lia Bittencourt, Sergio Tufik, José Haba-Rubio, Raphael Heinzer**

2016

	Points
Neck circumference	4
Obesity	
BMI 25 kg/m² to <30 kg/m²	3
BMI ≥30 kg/m²	5
Snoring	2
Age >55 years	4
Sex: male	2

The patient has a high probability of sleep-disordered breathing if they have a NoSAS score of 8 or higher. BMI=body-mass index.

***Table* 2: NoSAS score**

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Early CPAP improves outcome after stroke

n=55, CPAP=16

Outcome	Intention-to-Treat			Adherence Analysis†		
	Intervention (N = 31)	Control (N = 24)	P-value	No CPAP (N = 13)	Some CPAP (N = 6)	Acceptable CPAP (N = 10)
Stroke severity (NIHSS) median change from baseline to 30-days	−3.0	−1.0	0.03	−1.0	−2.5	−3.0
Vascular events*	1 (3.2)	3 (12.5)	0.31	2 (15.4)	0 (0)	0 (0)

10/16 pts with good adherence to CPAP
(>75%, >4 nights)

Bravata, Sleep 2011

J Sleep Res. (2014) Regular Research Paper

Efficacy of continuous positive airway pressure treatment on 5-year survival in patients with ischaemic stroke and obstructive sleep apnea: a randomized controlled trial

OLGA PARRA[1], ÁNGELES SÁNCHEZ-ARMENGOL[2], FRANCISCO CAPOTE[2], MARC BONNIN[1], ADRIÀ ARBOIX[3], FRANCISCO CAMPOS-RODRÍGUEZ[4], JOSÉ PÉREZ-RONCHEL[4], JOAQUÍN DURÁN-CANTOLLA[5], CRISTINA MARTÍNEZ-NULL[5], MÓNICA DE LA PEÑA[6], MARIA CARMEN JIMÉNEZ[7], FERNANDO MASA[4], IGNACIO CASADON[8], MARIA LUZ ALONSO[6] and JOSÉ L. MACARRÓN[6]

2014

5-year survival
stroke pts with AHI≥20

with early nCPAP (n=57)
without nCPAP (n=69)

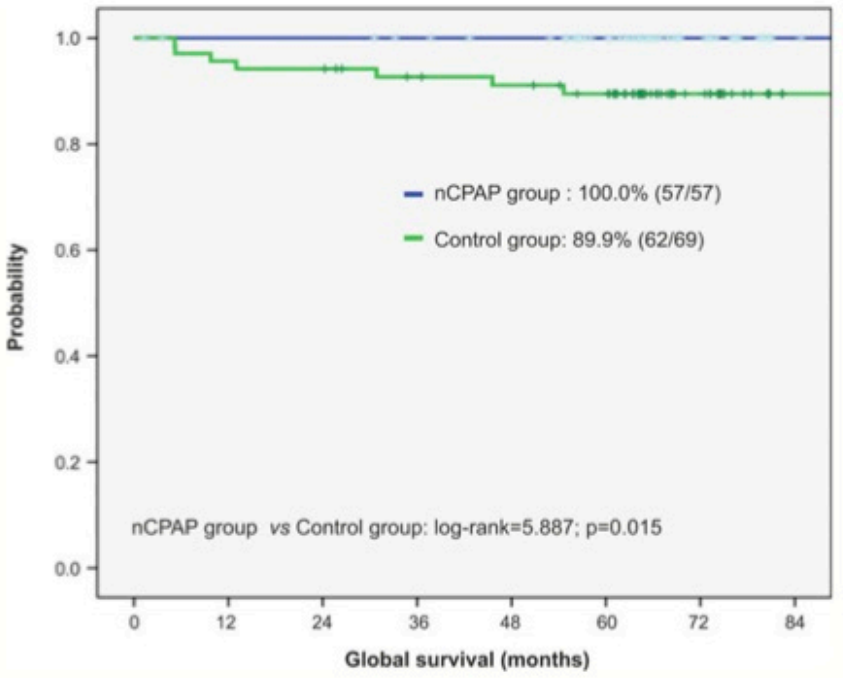
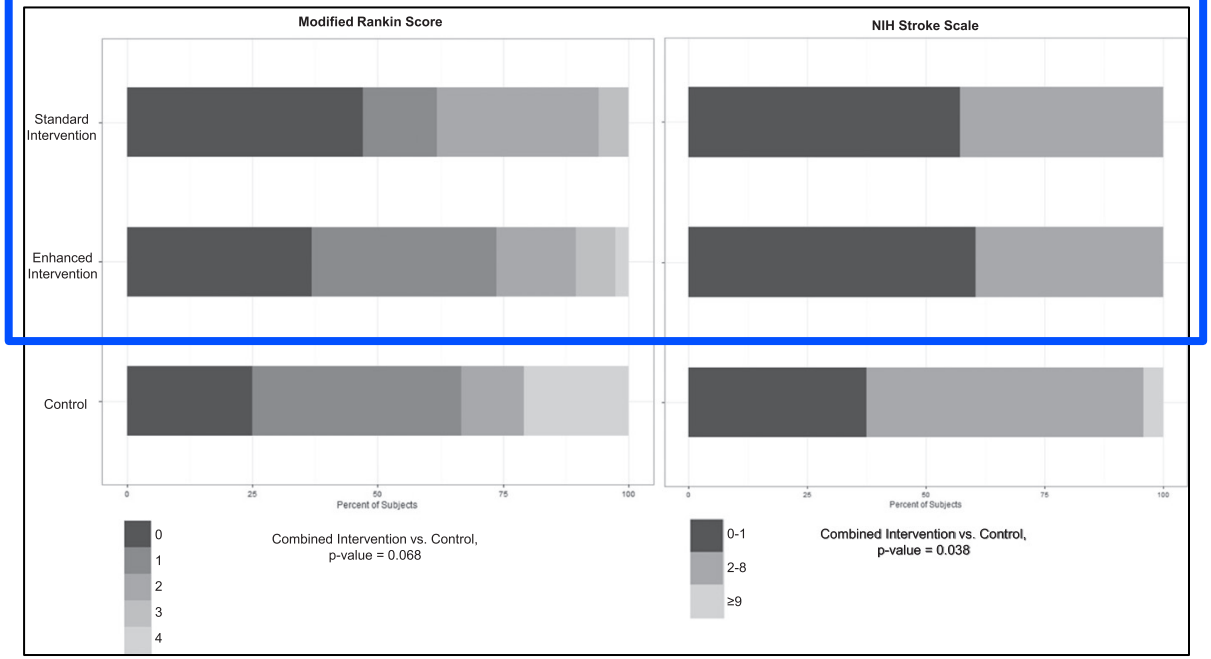


Figure 2. Cardiovascular survival [nasal continuous positive airway pressure (nCPAP) group and control group].

Diagnosing and Treating Sleep Apnea in Patients With Acute Cerebrovascular Disease

Dawn M. Bravata MD; Jason Sico, MD; Carlos A. Vaz Fragoso, MD; Edward J. Miech, EdD; Marianne S. Matthias, PhD; Rachel Lampert, MD; Linda S. Williams, MD; John Concato, MD; Cristina S. Ivan, MD; J. D. Fleck, MD; Lauren Tobias, MD; Charles Austin, MDiv; Jared Ferguson, BS; Radu Radulescu, MD; Lynne Iannone, MS; Susan Ofner, MS; Stanley Taylor, MA; Li Qin, PhD; Christine Won, MD; H. Klar Yaggi, MD

2018



RCT
n=252 enrolled
3 groups

auto-titrating CPAP
follow-up: 12 months

CPA-use>4h in 70%

Bravata, JACC 2018

Published Ahead of Print on March 9, 2018 as 10.1212/WNL.0000000000005262

ARTICLE

CPAP as treatment of sleep apnea after stroke

A meta-analysis of randomized trials

Anne-Kathrin Brill, MD,* Thomas Horvath, MD,* Andrea Seiler, MD, Millene Camilo, PhD, Alan G. Haynes, PhD, Sebastian R. Ott, MD, Matthias Egger, MD, and Claudio L. Bassetti, MD

Correspondence
Prof. Bassetti
claudio.bassetti@insel.ch

Neurology® 2018;0:e1-e9. doi:10.1212/WNL.0000000000005262

2019

Brill, Neurology 2019

1980-11.2016
Pubmed, Embase, Cochrane

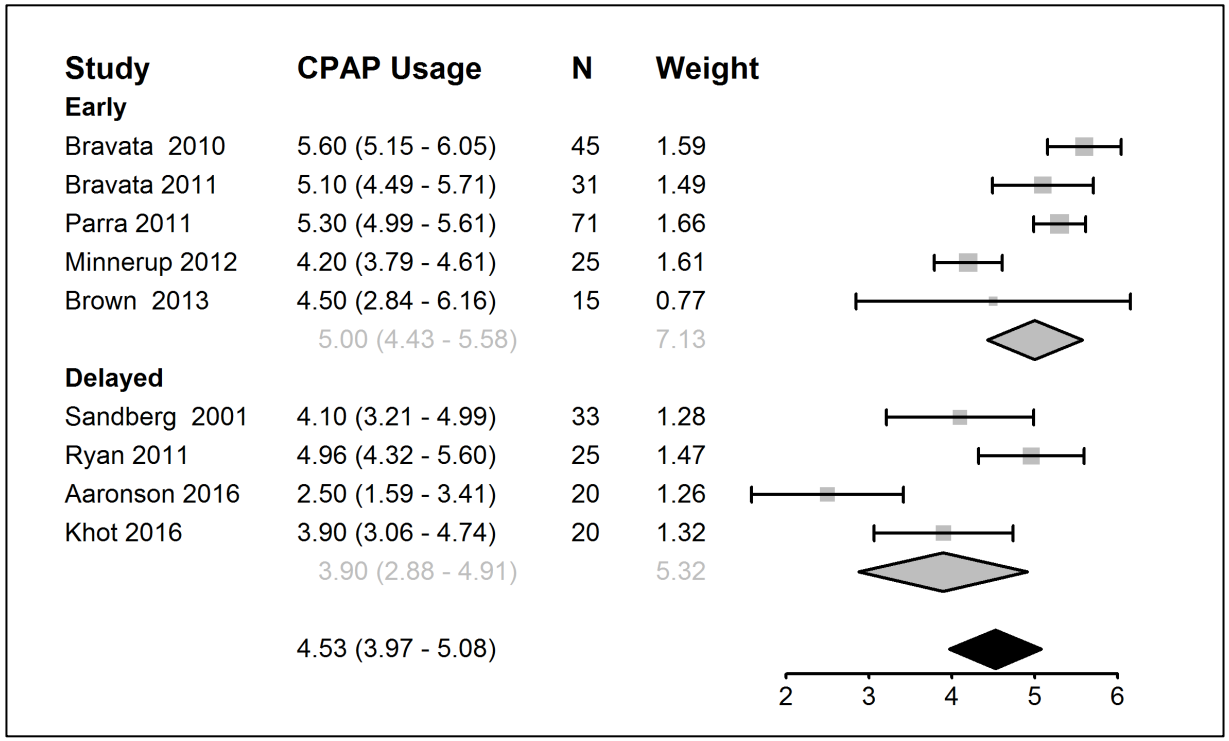
10 RCT`s
5 <1 week, 5 10-28 days
483 pts

PRISMA statement
Guidelines

CPAP Usage

9 studies, median usage: 4.5h

considerable heterogeneity (I^2=87%)

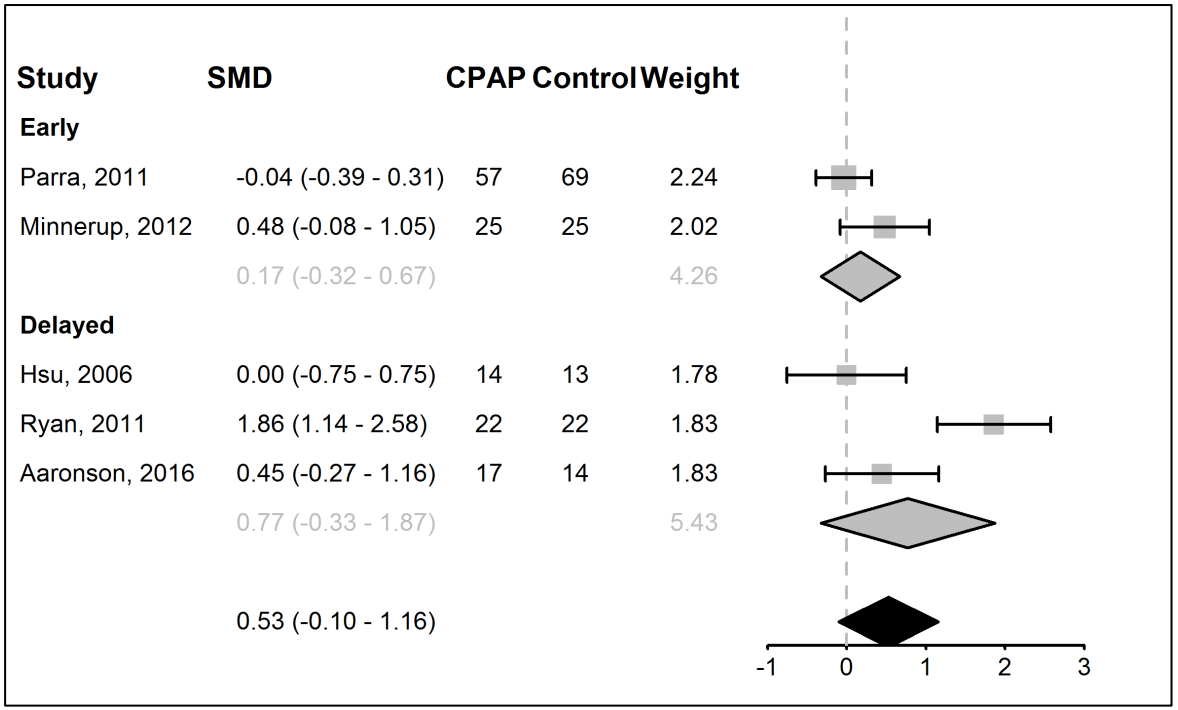


Neurological outcome

5 studies, NIHSS/CSS

trends to improvement (standardized mean difference 0.53)

considerable heterogeneity (I^2=82%)



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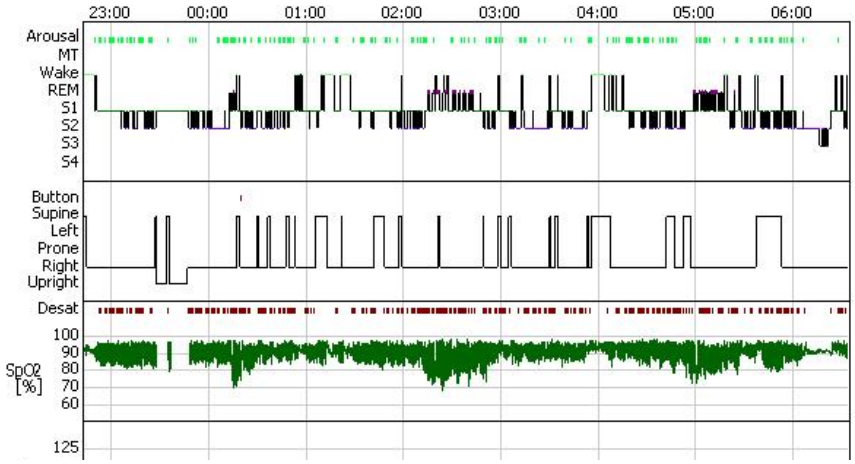
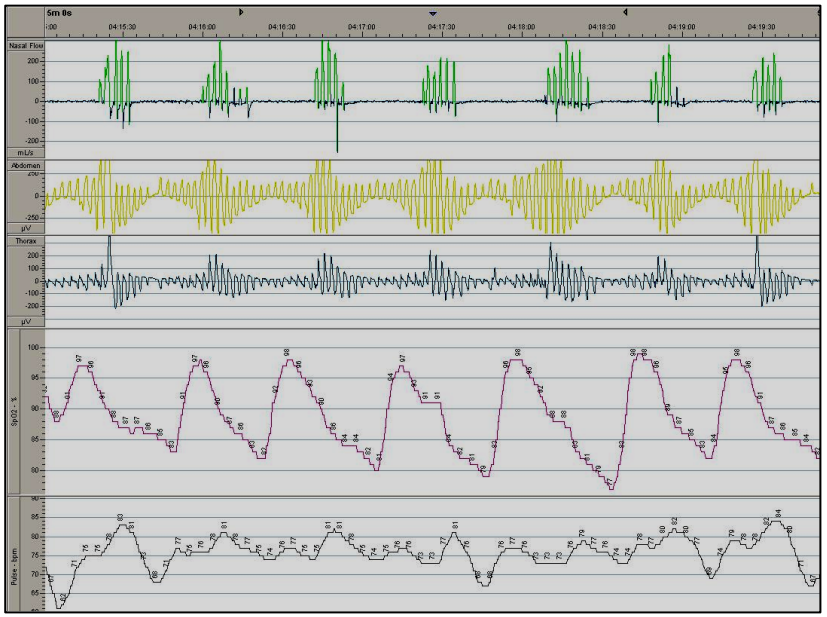
V.C., 70y male

Sleep study





Apnea-Hypopnea-Index: 72/h
85% obstructive events

<u>Desaturations</u>:
178 min <90%
16 min <80%

V.C., 70y male

The following statement is correct:

A. A sleep disordered breathing (SDB) is probable
B. The absence of sleepiness makes a SDB unlikely
C. The diagnosis of SDB in the stroke unit is difficult
D. The treatment of SDB in acute stroke patients is usually not possible and has no long-term effects

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SDB and stroke: Conclusions

- SDB is frequent in acute stroke (30% > 30/h)
- SDB has (probably) a negative effect on outcome

- Risk profile >> symptoms predicts SDB in stroke pts
- CPAP treatment in acute stroke is feasible
- CPAP may have a positive effect on stroke outcome