Physiologic Changes of Sleep Apnea with Age and Gender

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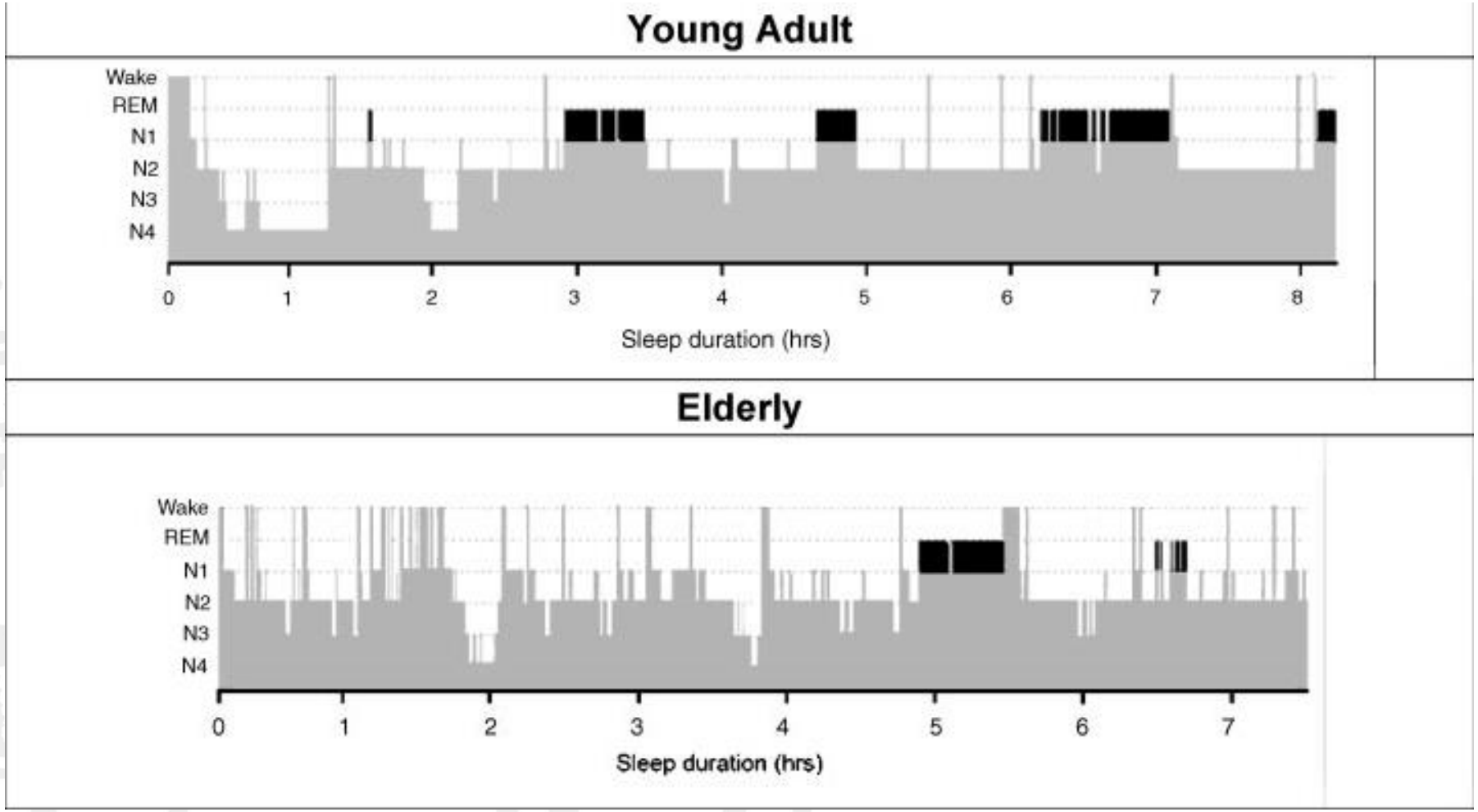
Sleep architecture as a function of age

	Percentage of Time Spent in Stage—Mean (95% CI)							
	Stage 1		Stage 2		Stages 3 + 4		REM Sleep	
Age (yr)	Men	Women	Men	Women	Men	Women	Men	Women
37-54	5.8 (5.2–6.5)	4.6 (4.1–5.3)	61.4 (60.0–62.8)	58.5 (57.1–60.0)	11.2 (9.9–12.6)	14.2 (12.7–15.9)	19.5 (18.8–20.2)	20.9 (20.0–21.8)
55-60	6.3 (5.6–7.0)	5.0 (4.4–5.7)	64.5 (63.2–65.9)	56.2 (54.5–57.8)	8.2 (7.1–9.5)	17.0 (15.2–18.9)	19.1 (18.4–19.8)	20.2 (19.3–21.1)
61-70	7.1 (6.4–7.9)	5.0 (4.4–5.7)	65.2 (63.9–66.5)	57.3 (55.7–58.9)	6.7 (5.7–7.7)	16.7 (14.8–18.6)	18.4 (17.8–19.1)	19.3 (18.4–20.2)
>70	7.6 (6.8–8.5)	4.9 (4.3–5.6)	66.5 (65.1–67.8)	57.1 (55.6–58.7)	5.5 (4.5–6.5)	17.2 (15.5–19.1)	17.8 (17.1–18.5)	18.8 (18.0–19.6)

Arch Intern Med 2004;164:406-18.

Effect of aging on the architecture of sleep



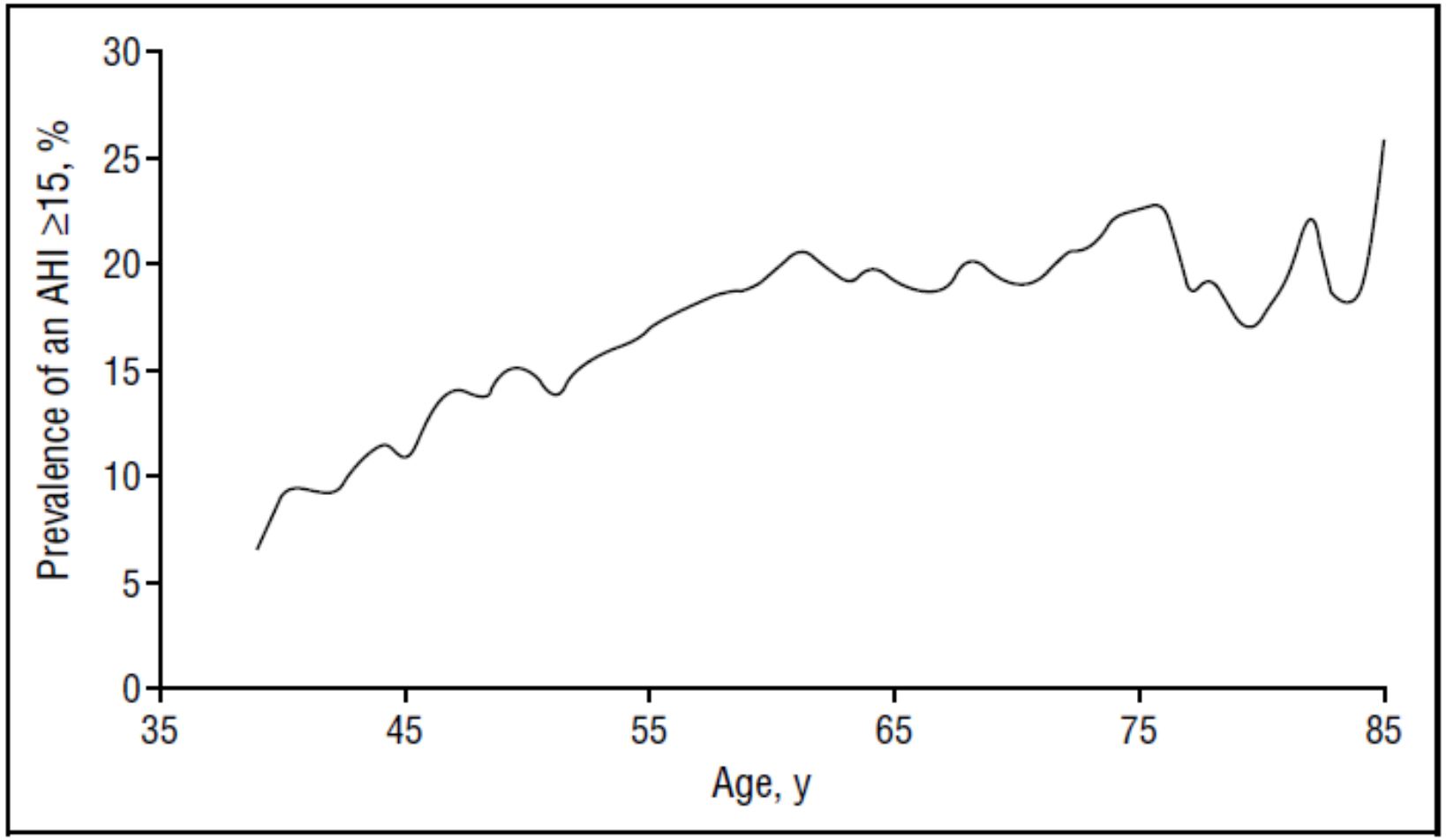
Semin Respir Crit Care Med 2010;31:618-33.

Typical changes in sleep patterns with age

Total sleep time decreases
Sleep onset or latency becomes delayed
Increased daytime napping
Increase in awakenings and arousals
Decreased sleep efficiency
Increased stage 1 and 2 sleep
Decreased stage 3 and 4 sleep or slow wave sleep (SWS)
Circadian phase advanced (i.e., early to bed and early to rise)
Decreased rapid-eye movement (REM) sleep
Fewer sleep cycles through per night

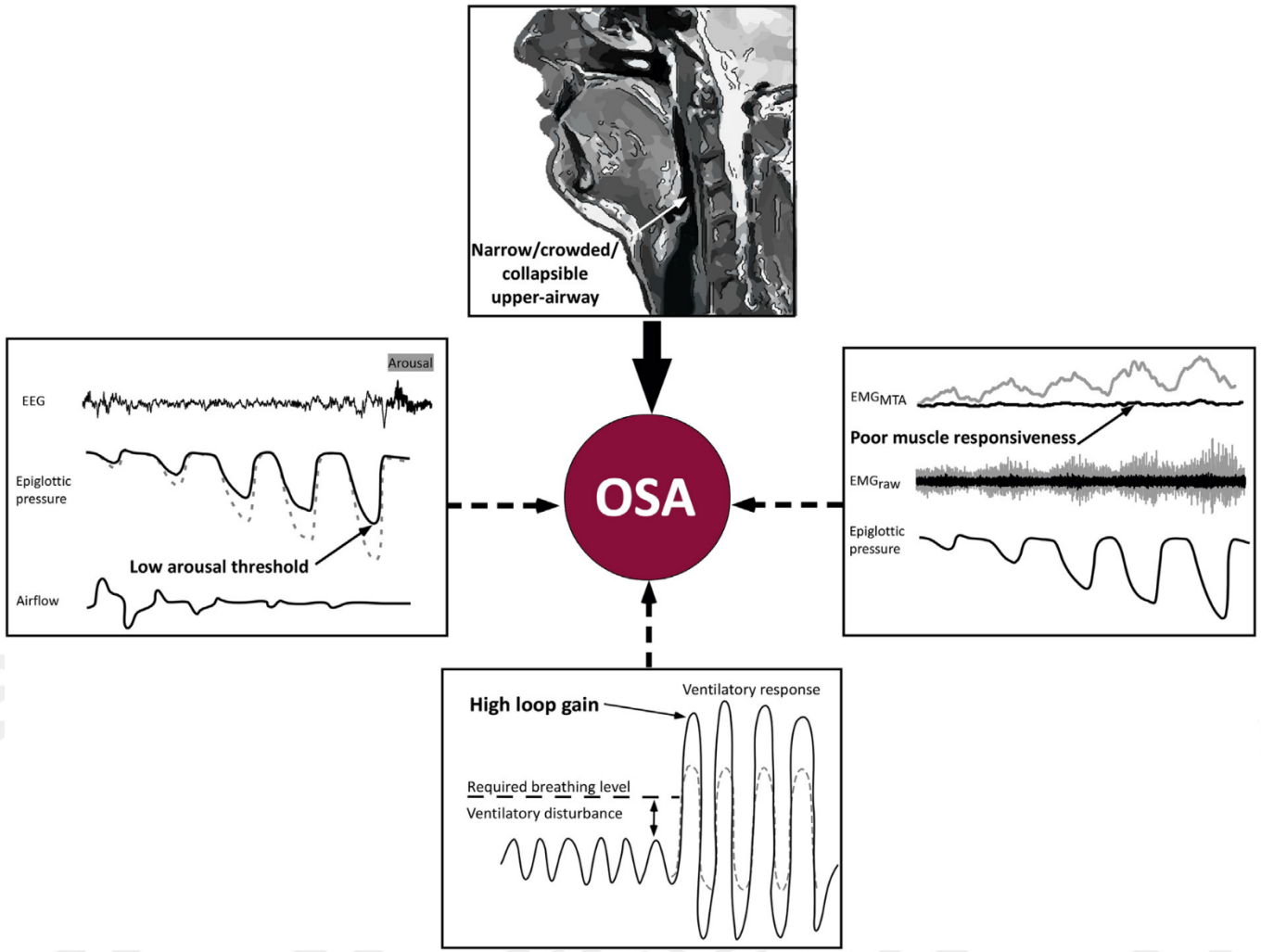
Semin Respir Crit Care Med 2010;31:618-33.

Prevalence of sleep-disordered breathing



Arch Intern Med 2002;162:893-900.

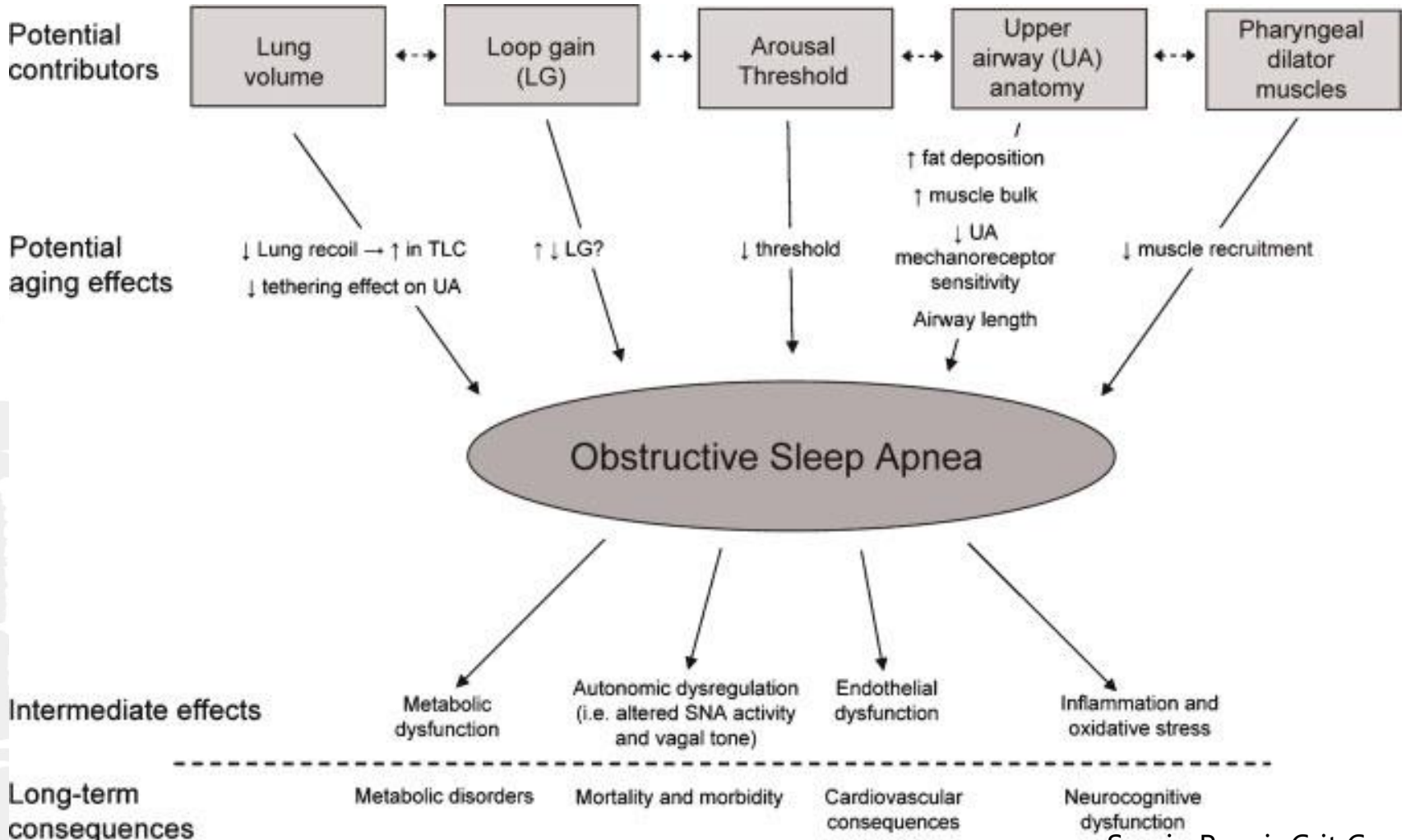
Pathophysiology of OSA



- Small & collapsible upper airway
- Poor upper airway muscle function
- Low arousal threshold
- Respiratory instability (high loop gain)

Lancet. 2014;383(9918):736-747.
Chest 2018;153:744-55.

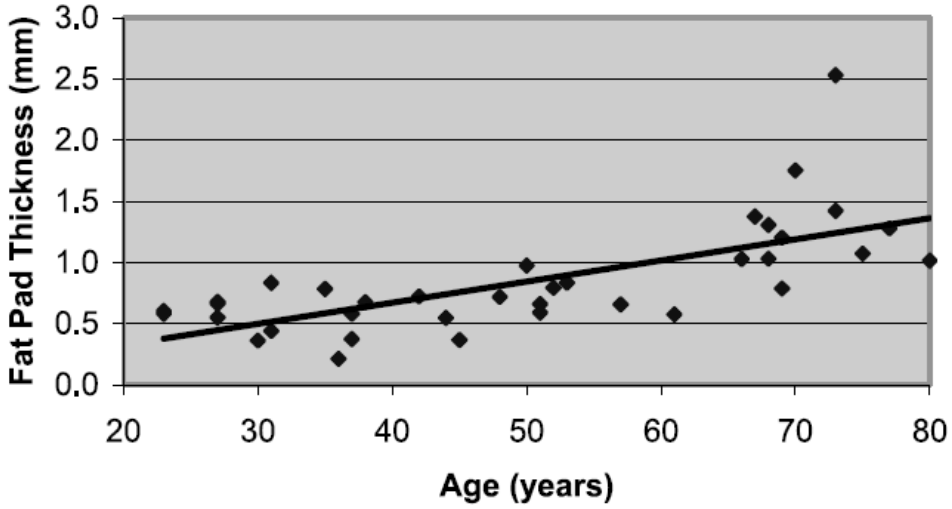
Effects of aging on the pathophysiology of OSA



Semin Respir Crit Care Med 2010;31:618-33.

Upper airway anatomy and collapsibility

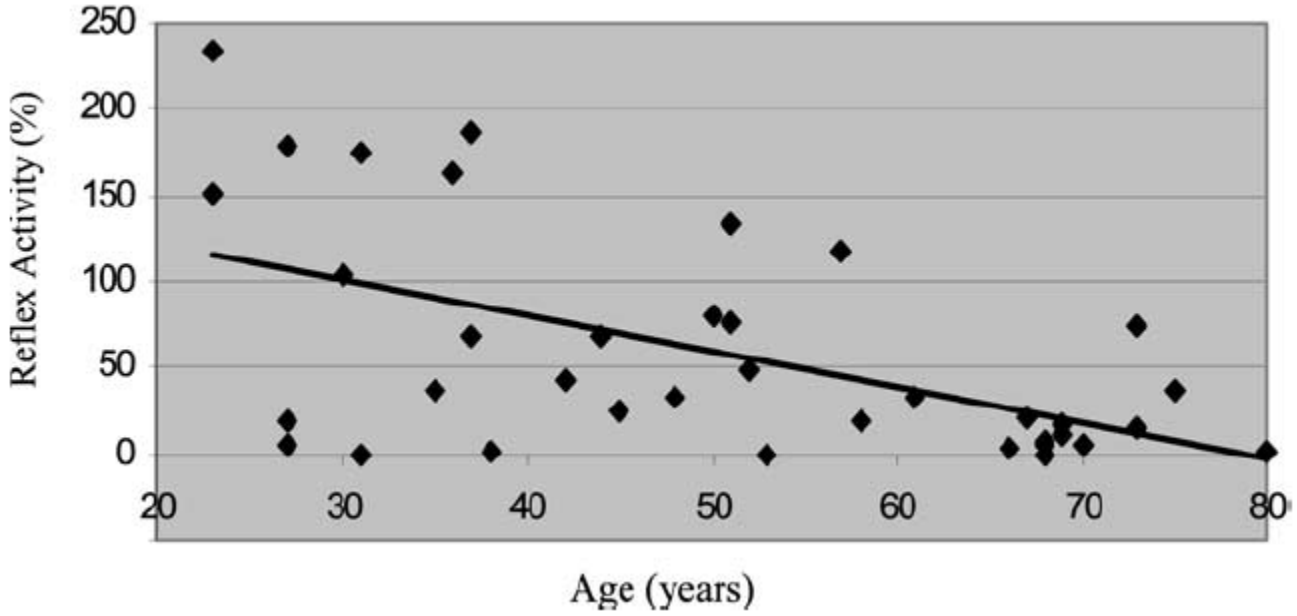
- A preferential deposition of parapharyngeal fat with aging.
- Increased pharyngeal collapsibility during sleep in older as compared with younger individuals.
- As the length of the airway increases, it becomes more prone to collapse (men, menopaused women).



Am J Med 2006;119:72.e9-14.

Upper airway dilator muscle activity

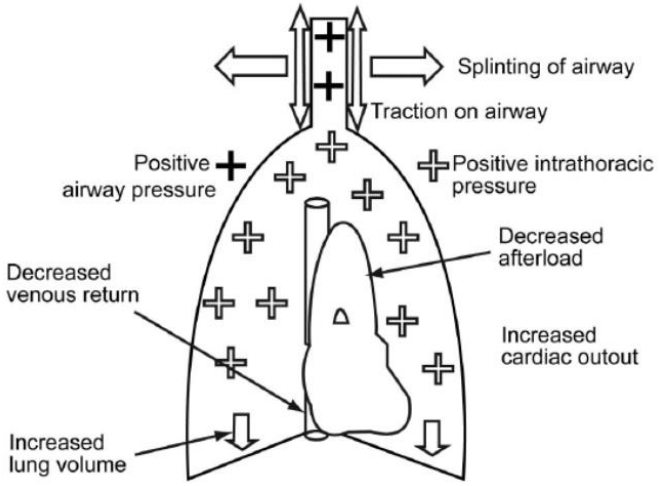
- The ability of the genioglossus muscle (the major pharyngeal dilator muscle) to respond to increases in pharyngeal negative pressure is impaired with aging, yielding a more vulnerable airway.



Am J Med 2006;119:72.e9-14.

Lung volume changes

- An increase in lung volume can apply a caudal traction force on the trachea and larynx.
- Such traction can induce longitudinal tension on the UA, reduce the intraluminal pressure required to close and reopen the UA, as well as decrease the pressure exerted on the UA walls by surrounding tissues, all of which may assist in patency.
- Lung compliance is known to increase with aging.
- Aging-related decrements in lung elastic recoil could compromise pharyngeal mechanics.
- Older individuals may have less lung volume tethering on the UA than younger individuals.

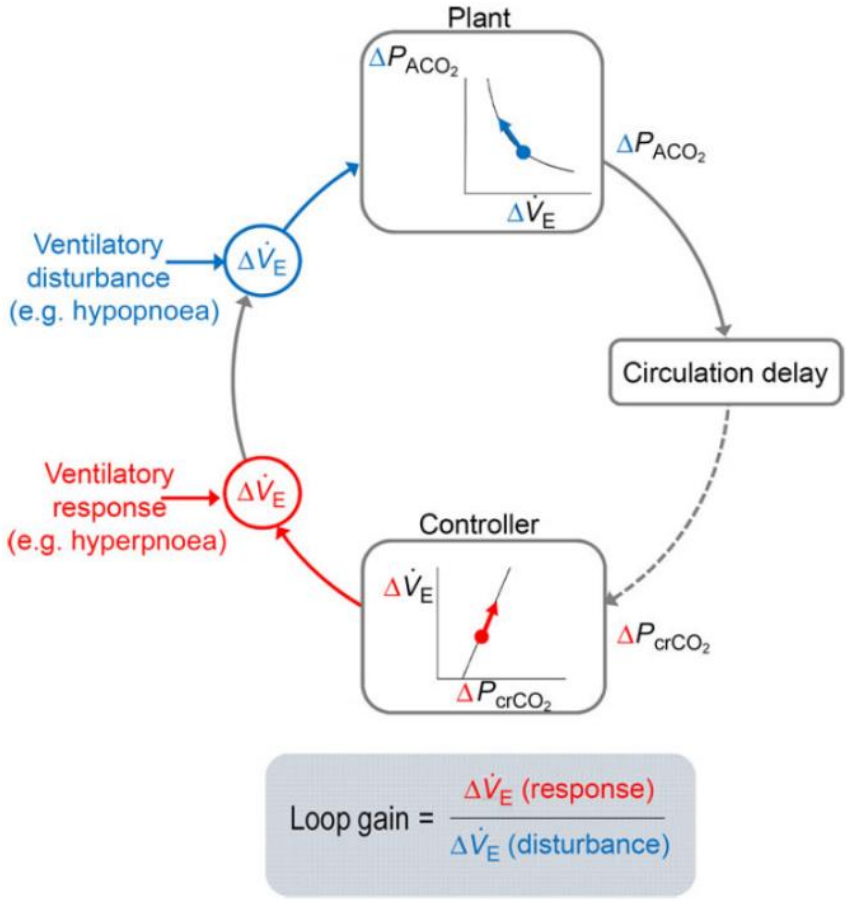


Arousal threshold

- Elderly people are known to have an increased number of spontaneous arousals from sleep, suggesting that older adults may have a lower arousal threshold.
- Recent studies examining how the arousal threshold changes with age have found no difference.
- Controversy remains regarding aging effects on arousal threshold.

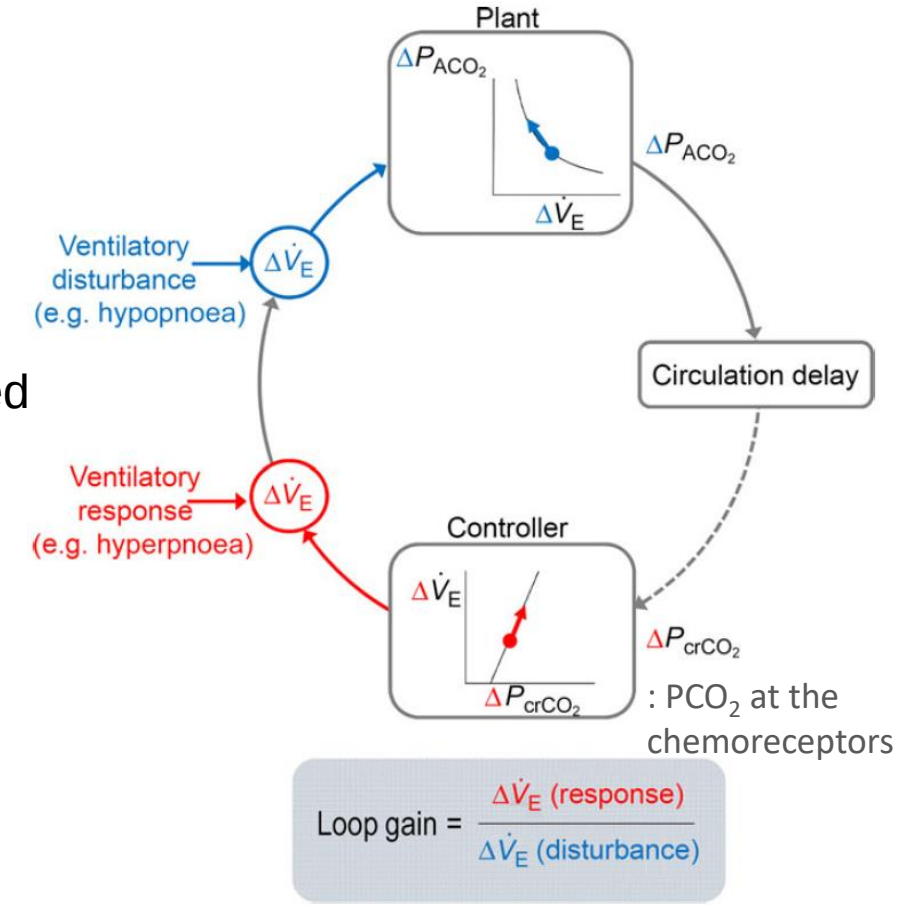
Ventilatory control stability or loop gain

- Controversy remains regarding aging effects on loop gain.
- There are several features of the ventilator pattern in elderly individuals which suggest that the chemical control of breathing is unstable.
  - an increased proportion of central apneas in elderly patients
- Chemosensitivity is actually unchanged. Ventilatory control is quite stable in the elderly.



Loop gain

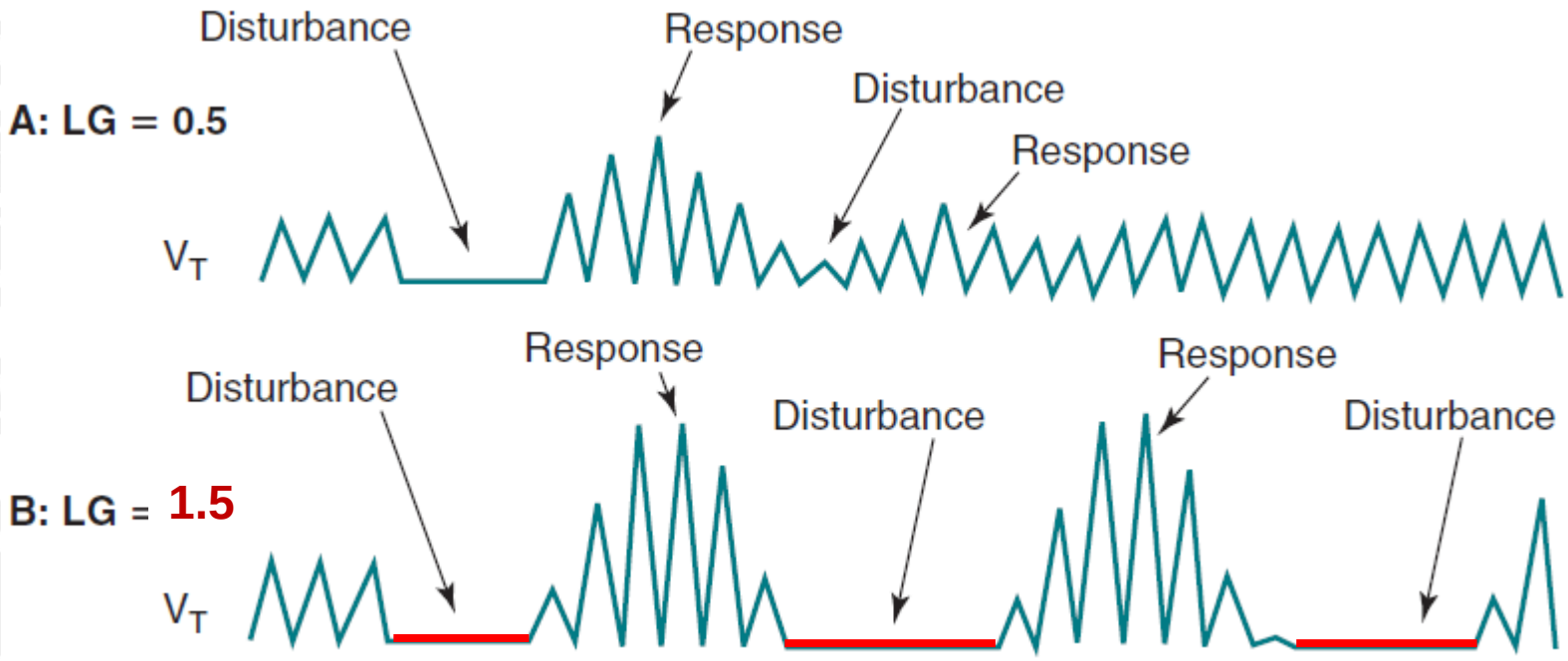
- **Loop gain**
  - ventilatory response to a disturbance of ventilation
  - **plant gain x controller gain**
- **Plant gain**
  - change in alveolar PCO_2 ($PACO_2$) for a given change in ventilation
  - Plant: lungs, blood, and body tissues where carbon dioxide is stored
- **Controller gain**
  - change in ventilation for a given change in arterial PCO_2 ($PaCO_2$)
  - Controller: all the structures responsible for converting chemoreceptor stimuli into ventilation
- **Circulation delay**
  - time it takes for pulmonary capillary blood to reach the chemoreceptors
  - primarily influenced by the cardiac output



J Physiol 2014;592:2903-5.

Loop gain

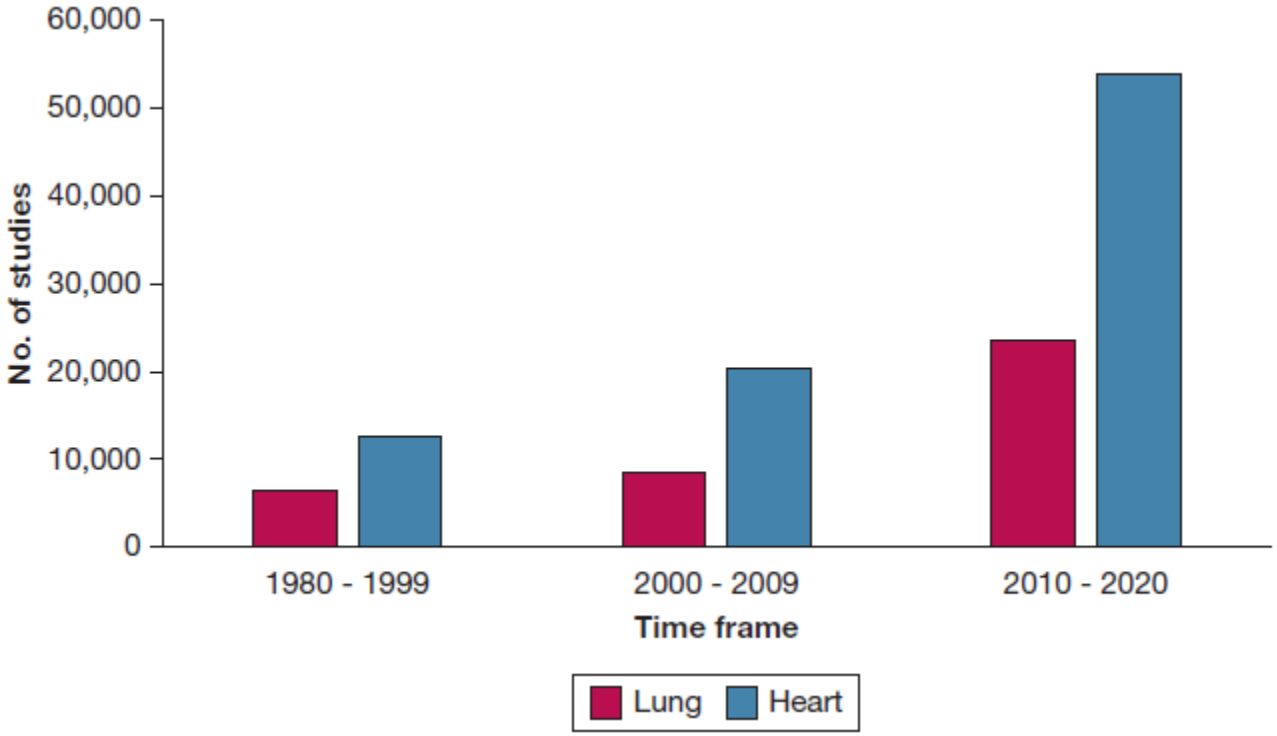
- Low loop gain (loop gain <1) → stable system
- High loop gain (loop gain >1) → unstable system



⇨ **apnea**

Fundamentals of sleep medicine, Chapter 21

Studies indexed in PubMed



Chest 2022;162:647-58.

Sex and gender terminology

Hormonal influences on asthma manifestation around puberty, pregnancy, and menopause are related to female sex.

Sex

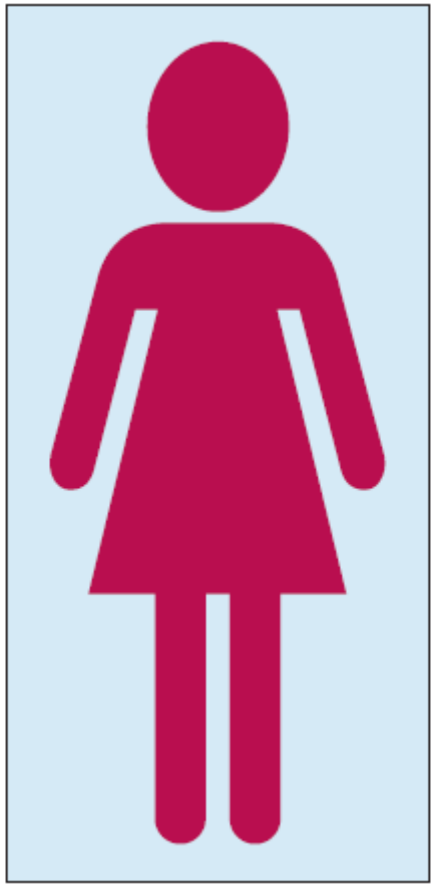
Endogenous Factors
- Sex hormones
- Reproductive events
  Puberty, menarche, pregnancy, postpartum, menopause

Anatomic Factors
- Lung size
- Airway size

Physiologic Factors
- Immune response
- Endotypes

Genetics
- Sex Chromosomes
- SNPs
- Sex-specific regulatory networks resulting from different hormonal exposures

Genome Regulation
- Gene expression



Gender

Exogenous Factors
- Socioeconomic status
- Education
- Environmental exposure
- Occupational exposure
- Exogenous hormone exposure
- Smoking

Access factors
- Access to health care
- Health seeking behaviors
- Preventative care

Individual Factors
- Risk taking behavior

Epigenetics
- DNA modification (methylation)
- Chromatin accessibility
- Microbiome

The impact of biomass fuel on lung physiology and disease in women in low-income countries is related to women's societal role, and therefore is a gender effect.

Chest 2022;162:647-58.

Sex and gender differences in common respiratory diseases

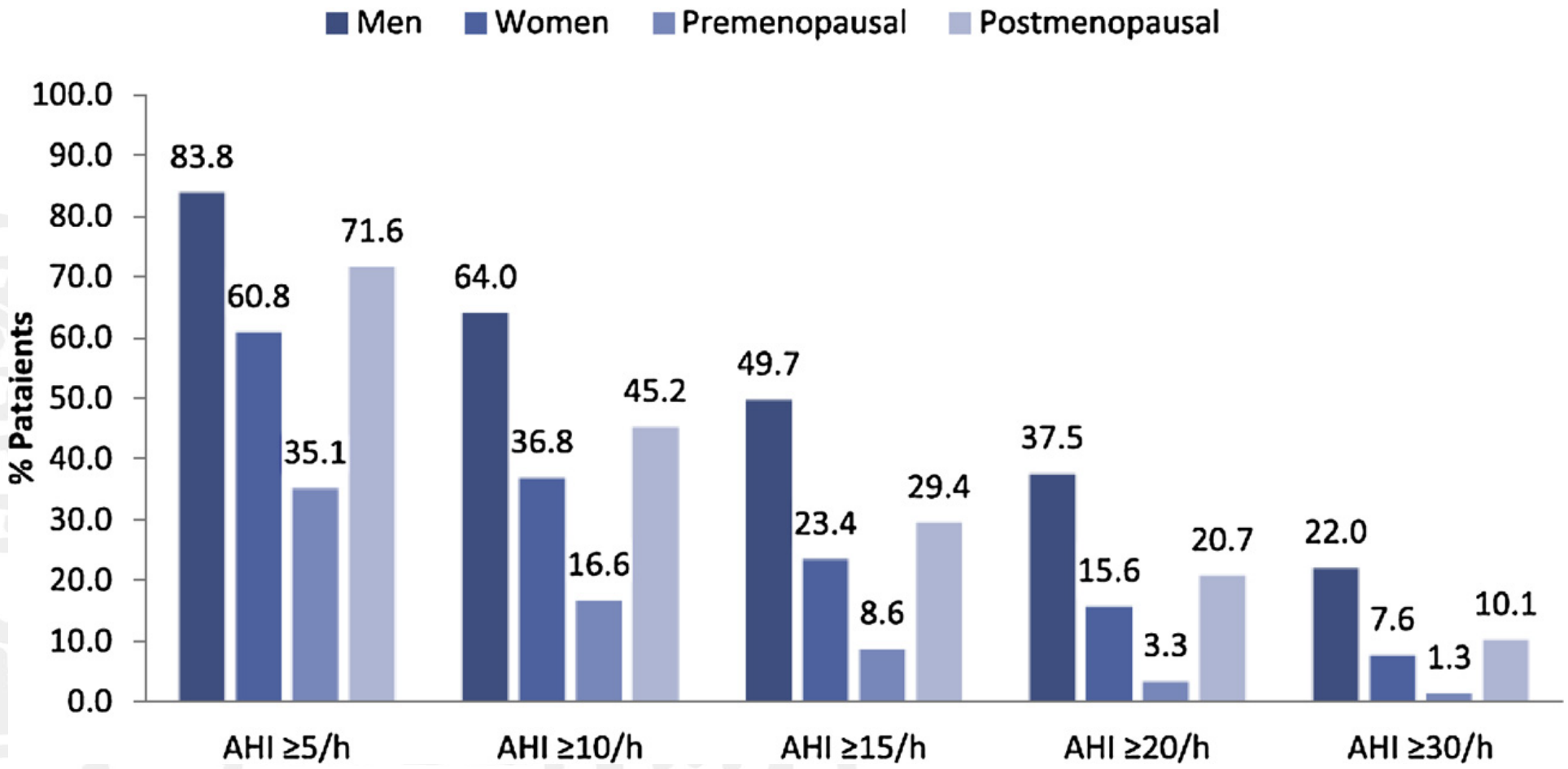
Disease	Sex Differences		Gender Differences, Women vs Men
	Male Sex	Female Sex	
COPD	Higher prevalence	Early onset with less tobacco exposure, majority of nonsmoking COPD, high exacerbation rates, immune dysregulation, higher annual decline in DLCO, decline in lung function at menopause, more anxiety and depression, poorer QoL	Increased advertisements aimed at women in the 1960s; increased smoking rates; often misdiagnosed; presence of comorbid conditions, anxiety, and depression
Asthma	Higher prevalence before puberty	Higher prevalence after puberty, perimenstrual asthma, less likely to receive pharmacotherapy, worse perception of symptoms, worse QoL despite similar baseline severity, potentially improves after menopause, HRT has conflicting results on asthma incidence during menopause	Occupational exposures may worsen asthma features, more obesity, and GERD; often misdiagnosed; prescribed psychotropic medications more often
Lung cancer	Higher incidence and mortality; some studies suggest better response to immunotherapy, but not consistent	Potentially more susceptible to cigarette smoke; represent most cancers in nonsmokers; underrepresented in screening studies; may need different screening guidelines; may have more benefit from screening; better overall response to therapy; overall better survival after adjusting for tumor type, age, and smoking status	Targeted smoking campaigns, increased smoking rates, more difficulty in quitting smoking, exposure to second- and third-hand smoke, higher exposure in certain occupations, potentially higher environmental exposure, misdiagnosis or later diagnosis
ILD	IPF is more common, mortality higher, more prone to fibrosis developing in CTD-ILD and poorer prognosis	Hypersensitivity pneumonitis and sarcoidosis are more common, CTD-ILD more common, less fibrosis in CTD-ILD, IPF mortality lower, lymphangioleiomyomatosis occurs almost exclusively	Report more dyspnea for same severity of disease in IPF, dyspnea impacts emotional health-related QoL more in women with IPF, poorer QoL in sarcoidosis, poorer QoL in RA-ILD, time to treatment initiation for IPF and other ILD longer
OSA	Higher overall AHI, lower oxygen saturation	REM predominant OSA, worsens with age and menopause, more frequent arousals from sleep, incidence increased in menopause (especially if not receiving HRT)	Fatigue and insomnia, rather than snoring and sleepiness may be predominant symptoms; screening questionnaires such as STOP-BANG favor men; very limited data on response to different treatments between men and women

Anatomic and physiological differences between the sexes

Lower in Women	Higher in Women	Equal in Both Sexes
TLC (corrected for height)	Expiratory flow limitation	Respiratory rate
Tidal volume (corrected for height), minute ventilation (corrected for height)	Resistive work of breathing	Viscoelastic work of breathing
Peak inspiratory flow (corrected for height), peak expiratory flow (corrected for height)	Dyspnea rating (for given minute ventilation)	No. of alveoli per unit volume
Airway size (height matched)	. . .	. . .
Tracheal diameter (matched for TLC)	. . .	. . .
Pharyngeal airway length	. . .	. . .

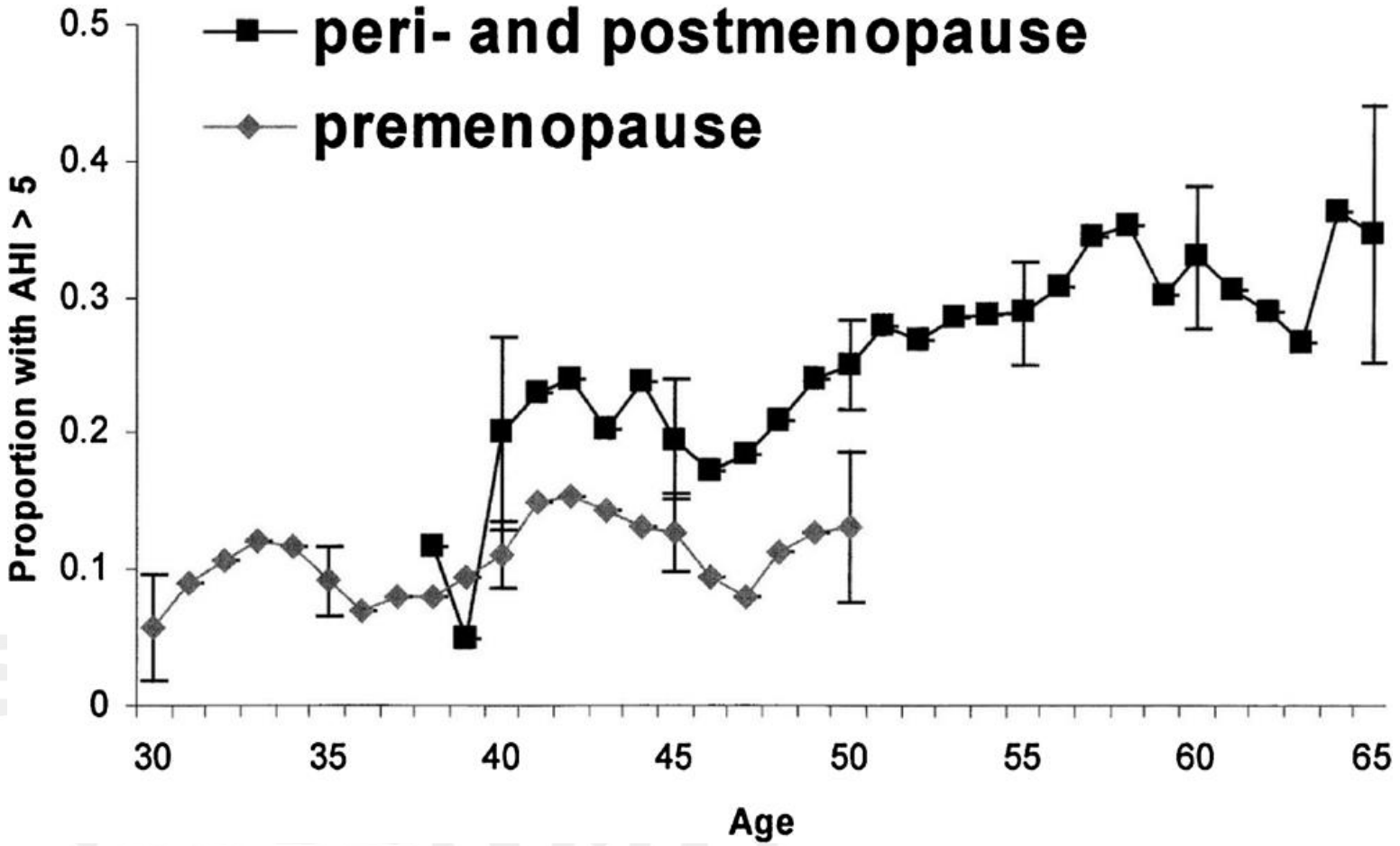
Chest 2022;162:647-58.

Prevalence of sleep-disordered breathing

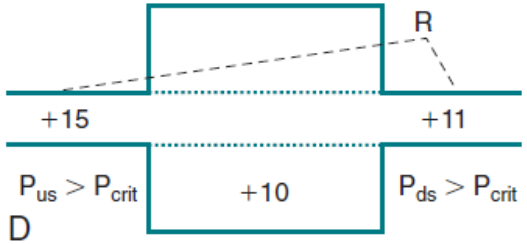


Sleep Med 2018;51:29-36.

Menopause and sleep apnea



Am J Respir Crit Care Med 2003;167:1181-5.

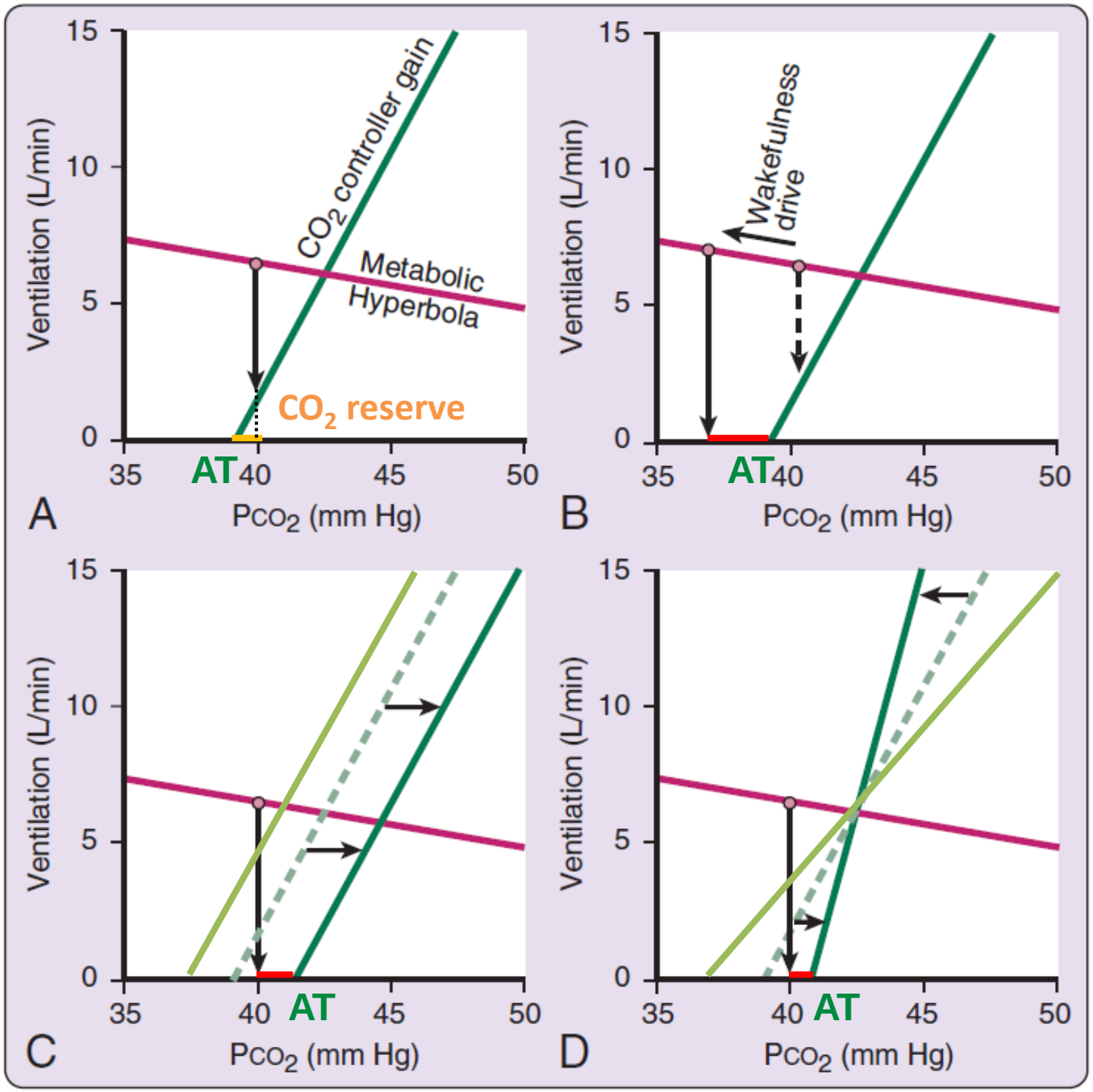


Pathophysiology of OSA/OSAHS

Upper airway less collapsible
Shorter airway length, which increases with age
Lower critical closing pressure
Subcutaneous and peripheral fat distribution
Prolonged partial upper airway obstruction leading to increased respiratory resistance, increased end-tidal CO_2
Lower chemoresponsiveness
Lower metabolic rate
Less respiratory drive instability
Progesterone stimulates ventilation
Higher CO_2 sensitivity and lower upper airway resistance during the luteal phase of menstrual cycle (high progesterone levels)
Premenopausal females have lower apnoeic thresholds

In pregnancy

Reduction in airway size, fluid retention, weight gain, nasal obstruction
Reduced functional respiratory capacity and residual volume
Increased minute ventilation
High progesterone leading to increased upper airway dilator muscle activity
Enhanced chemoreceptor responsiveness
Right-shifted oxygen dissociation curve
Increased maternal heart rate and stroke volume
Less time in the supine position



AT = apneic threshold

CO_2 reserve = eupneic CO_2 – AT CO_2

A. At sleep onset

B. Wakefulness drive ↑

C. Plant gain↑/ ↓

D. Controller gain↑ (e.g. CHF) / ↓

Principles and Practice of Sleep Medicine, 5th ed., Chapter 100

Clinical presentation	
Overall	More likely to present with insomnia, mood disturbances, nightmares, fatigue, lack of energy Greater impairment of quality of life Higher healthcare expenditure Higher rate of sick leave, impaired work performance, divorce Hypothyroidism more common Less intense snoring
Pregnancy	Increased snoring as pregnancy progresses Snoring/OSA associated with pregnancy-induced hypertension, intra-uterine growth retardation, hypertension and diabetes mellitus
Menopause	Clinical presentation attributed to menopause Doubling of OSA/OSAHS prevalence in menopause
Findings on sleep studies (polysomnography/polygraphy)	Lower AHI overall Shorter apnoeic episodes More frequent subcriterion events Lower proportion of supine OSA Higher frequency of REM-related OSA Longest apnoeas associated with more severe arterial oxygen desaturation Increased sleep fragmentation in pregnancy

Associations sleep questionnaires with OSA (REI > 15) stratified by gender

	Gender			
	Male		Female	
	OR (CI 95%)	*p*	OR (CI 95%)	*p*
Snoring (yes/no)	**3.02 (1.06–8.6)**	**0.04**	1.53 (0.58–3.98)	0.4
Apneas (yes/no)	**3.3 (1.9–5.77)**	**<0.001**	**2.32 (1.4–3.87)**	**0.001**
ESS	1.06 (0.97–1.16)	0.18	**1.17 (0.06–1.28)**	**0.001**
Berlin	**3.66 (1.05–12.7)**	**0.04**	5.5 (0.19–15)	0.3
STOP	0.78 (0.29–1.8)	0.5	3.2 (1.16–8.9)	0.025
STOP-BANG	1.47 (0.7–3.1)	0.3	0.5 (0.26–1.14)	0.11

J Clin Med 2020;9.

Menopause: The Journal of The North American Menopause Society
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Short-term medroxyprogesterone acetate in postmenopausal women with sleep-disordered breathing: a placebo-controlled, randomized, double-blind, parallel-group study

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Abstract

Objective: Menopause predisposes women to sleep-disordered breathing (SDB) and sleep disturbances. Progestin has a potential to stimulate breathing and to induce sleep. Our goal was to test these effects objectively and to compare them with the effects of nasal continuous positive airway pressure (CPAP), which is the standard treatment of SDB.

Methods: In a placebo-controlled, double-blind, parallel-group trial, we investigated 34 postmenopausal women (17 in the placebo group and 17 in the medroxyprogesterone acetate [MPA] group) whose SDB had been treated with nasal CPAP for 6 months to 8 years prior to study entry. The 6-week trial included measurements with CPAP at baseline, after 14 days of placebo or MPA (60 mg daily), and after a 3-week washout. The participants discontinued their nasal CPAP therapy 1 week after baseline measurements and went on with study medication.

Results: Two weeks after discontinuation of CPAP therapy, nightly oxygen saturation was sustained higher ($P = 0.004$) and arterial carbon dioxide tension was lower ($P < 0.001$) with MPA than with placebo. Carbon dioxide was also lower than during CPAP ($P < 0.001$), and this effect was sustained beyond 3 weeks after the cessation of MPA ($P < 0.001$). However, the apnea-hypopnea index of CPAP increased and sleep deteriorated similarly on MPA and placebo after withdrawal of CPAP therapy.

Conclusions: In postmenopausal women with SDB, MPA induces a long-lasting stimulatory effect on breathing without improving sleep quality or the apnea-hypopnea index.

Key Words: Postmenopausal women – Medroxyprogesterone acetate – Sleep-disordered breathing.

Study of a Novel APAP Algorithm for the Treatment of Obstructive Sleep Apnea in Women

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Study Objectives: To assess the efficacy of a novel female-specific autotitrating continuous positive airway pressure (CPAP) algorithm (AutoSet for her, AfH) in premenopausal women relative to a standard autotitrating algorithm (AutoSet, S9) (ResMed Ltd., Bella Vista, New South Wales, Australia).
Design: Prospective randomised crossover noninferiority trial.
Setting: Tertiary hospital sleep clinic and university research sleep laboratory.
Participants: 20 female patients with obstructive sleep apnea (OSA) established on long-term CPAP treatment.
Interventions: Treatment with 1 night each of AfH and AutoSet while monitored with overnight laboratory-based polysomnography (PSG); order randomly allocated.
Measurements and Results: The primary outcome variables were the apnea-hypopnea index (AHI) and 3% oxygen desaturation index (ODI 3%) determined from PSG. Treatment efficacy on the AfH night was noninferior to the AutoSet night as assessed by median (IQR) AHI (1.2 [0.60–1.85]/h versus 1.15 [0.40–2.85]/h, respectively, P = 0.51) and 3% ODI (0.85 [0.25–1.5]/h versus 0.5 [0.25–2.55]/h, respectively, P = 0.83). Other PSG measures were similar, except for the percentage of the night spent in flow limitation, which was lower on the AfH (0.14%) than the AutoSet night (0.19%, P = 0.007). The device-downloaded 95th centile pressure on the AfH night was also lower than on the AutoSet night (10.6 ± 1.7 versus 11.6 ± 2.6 cmH_2O, respectively; mean difference [95% confidence interval]: −1.1 [−2.13 to −0.01] cm H_2O).
Conclusion: Among premenopausal women a novel female-specific autotitrating algorithm (AfH) is as effective as the standard AutoSet algorithm in controlling obstructive sleep apnea (OSA). The new algorithm may reduce flow limitation more than the standard algorithm and achieve control of OSA at a lower (95th centile) pressure.

Summary

- OSA in the elderly can primarily be attributed to changes in the anatomy and physiology of the upper airway.
- Female with OSA appear to have more prolonged partial upper airway obstruction as a pathophysiological hallmark of their disorder.
- Women with OSA are less likely to snore and report sleepiness compared with men and are more likely to report fatigue and insomnia. Women were less likely to be referred for a sleep evaluation.
- The rise in OSA prevalence after menopause is likely in part the result of hormonal changes and increasing central obesity associated with menopause, but this is not completely clear yet.

Thanks for your attention