Title

Obstructive Sleep Apnea in Older Adults is a Distinctly Different Physiological Phenotype

Journal

Sleep, 37(7)

ISSN

0161-8105

Authors

Edwards, Bradley A

Wellman, Andrew

Sands, Scott A

et al.

Publication Date

2014-07-01

DOI

10.5665/sleep.3844

Peer reviewed

http://dx.doi.org/10.5665/sleep.3844

Obstructive Sleep Apnea in Older Adults is a Distinctly Different Physiological Phenotype

Bradley A. Edwards, PhD[1]; Andrew Wellman, MD, PhD[1]; Scott A. Sands, PhD[1]; Robert L. Owens, MD[1]; Danny J. Eckert, PhD[1,2]; David P. White, MD[1]; Atul Malhotra, MD[1,3]

[1]Division of Sleep Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [2]Neuroscience Research Australia (NeuRA) and the University of New South Wales, Randwick, Sydney, New South Wales, Australia; [3]Division of Pulmonary and Critical Care Medicine, University of California San Diego, San Diego, CA

Study Objectives: Current evidence suggests that the pathological mechanisms underlying obstructive sleep apnea (OSA) are altered with age. However, previous studies examining individual physiological traits known to contribute to OSA pathogenesis have been assessed in isolation, primarily in healthy individuals.

Design: We assessed the four physiological traits responsible for OSA in a group of young and old patients with OSA.

Setting: Sleep research laboratory.

Participants: Ten young (20-40 y) and old (60 y and older) patients with OSA matched by body mass index and sex.

Measurements and Results: Pharyngeal anatomy/collapsibility, loop gain (LG), upper airway muscle responsiveness/gain (UAG) and the respiratory arousal threshold were determined using multiple 2- to 3-min decreases or drops in continuous positive airway pressure (CPAP). Passive pharyngeal anatomy/collapsibility was quantified as the ventilation at CPAP = 0 cmH_2O immediately after the CPAP drop. LG was defined as the ratio of the ventilatory overshoot to the preceding reduction in ventilation. UAG was taken as the ratio of the increase in ventilation to the increase in ventilatory drive across the pressure drop. Arousal threshold was estimated as the ventilatory drive that caused arousal. V_{eupnea} was quantified as the mean ventilation prior to the pressure drop. In comparison with younger patients with OSA, older patients had a more collapsible airway (ventilation at 0 cmH_2O = 3.4 ± 0.9 versus 1.5 ± 0.7 L/min; P = 0.05) but lower V_{eupnea} (8.2 ± 0.5 versus 6.1 ± 0.4 L/min; P < 0.01) and a lower LG (5.0 ± 0.7 versus 2.9 ± 0.5; P < 0.05). The remaining traits were similar between groups.

Conclusions: Our data suggest that airway anatomy/collapsibility plays a relatively greater pathogenic role in older adults, whereas a sensitive ventilatory control system is a more prominent trait in younger adults with obstructive sleep apnea.

Keywords: aging, loop gain, lung, obstructive sleep apnea, sleep disordered breathing, upper airway collapsibility

Citation: Edwards BA, Wellman A, Sands SA, Owens RL, Eckert DJ, White DP, Malhotra A. Obstructive sleep apnea in older adults is a distinctly different physiological phenotype. *SLEEP* 2014;37(7):1227-1236.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive collapse or obstruction of the pharyngeal airway during sleep.[1] The resultant hypoxemia/hypercapnia, sympathetic activation, and sleep disruption often lead to impaired neurocognitive function and excessive daytime sleepiness.[2] Furthermore, patients with OSA are at higher risk of cardiovascular diseases, including hypertension, myocardial infarction, stroke, and heart failure, making it a major health problem.[3,4]

Aging is known to be an important factor contributing to the risk of OSA, with rising disease prevalence across a wide spectrum of ages.[5] Of note, a recent large study demonstrated that 50% of older men had a respiratory disturbance index > 13/h, with aging being an independent risk factor in multivariate logistic regression analyses.[6] In some but not all studies, OSA is a cause of increased mortality in older adults, with one large study demonstrating that patients older than 70 y with severe OSA have a significantly shorter survival time.[7] However, the mechanisms whereby aging increases the risk of OSA are not completely understood. OSA occurrence with aging may be driven by one or more of the physiological characteristics known to be important in OSA pathogenesis, with four of the most recognized factors being a poor upper airway anatomy (i.e. a highly collapsible airway), ineffective upper airway dilator muscle activity/responsiveness, a low respiratory arousal threshold, or an unstable ventilatory control system.[8–10]

Prior studies, limited primarily to healthy individuals (i.e., without OSA), have suggested that upper airway collapsibility worsens with age[11,12] and that the ventilatory control system becomes more stable.[13] Furthermore, older subjects tend to have an increased frequency of spontaneous arousals[14] (i.e., suggestive of a lower arousal threshold) and reduced upper airway muscle reflex response to negative pressure[15] in comparison with their younger counterparts. Collectively, these changes with aging in healthy individuals suggest that OSA might be caused by different mechanisms in older versus younger individuals. Since previous studies examined individual physiological traits in isolation, mainly in healthy individuals, this concept has not been adequately investigated. Accordingly, using a recently validated technique,[8] the current study aims to investigate the effect of aging on four key traits responsible for OSA in a group of young and older patients with OSA. Preliminary results of this analysis have been published in abstract form.[16]

Submitted for publication September, 2013
Submitted in final revised form January, 2014
Accepted for publication February, 2014

Address correspondence to: Bradley A. Edwards, PhD, Sleep Disorders Research Program, Division of Sleep Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; Tel: (617) 732-8456; Fax: (617) 732-7337; E-mail: baedwards@partners.org

METHODS

Participants

Ten relatively young (20-40 y) and ten older (60 y and older) body mass index (BMI) and sex-matched (matched on group means) patients with OSA were recruited from our sleep clinic. All subjects had a history of OSA with an apnea/hypopnea index (AHI) > 10 events/h during supine non-rapid eye movement (NREM) sleep and were treated with continuous positive airway pressure (CPAP) for more than 5 h per night for at least 2 mo prior to enrollment. Written, informed consent was given before participation in the study, which was approved by the Human Research Committee at Brigham and Women's Hospital. Subjects were excluded if they had a history of renal failure, neuromuscular disease or other major neurological disorders, uncontrolled diabetes, heart failure, central sleep apnea/Cheyne-Stokes respiration, uncontrolled hypertension, thyroid disease, or any other unstable medical condition. Female subjects were also screened to ensure that they were not pregnant. Of the young subjects, one was on a medication to lower cholesterol and another was taking an antihypertensive medication. In the elderly subjects, three subjects were receiving antihypertensive medications, two were on medications to lower cholesterol, two were on medications to treat arthritis, and one was taking medications for gastroesophageal reflux disease and depression. An important consideration in our experimental design was whether to study patients who are untreated or patients who are currently treated with CPAP therapy; several studies[17,18] have recently demonstrated that some of the phenotypic traits are altered as a consequence of disease and that studying compliant CPAP users (after at least 1 mo of therapy) allows a patient's intrinsic physiology to be determined. As the aim of the study was to examine changes in the intrinsic physiological traits with age rather than the degree to which the traits are affected by OSA *per se* and its progression, we studied patients who were CPAP compliant.

Experimental Design and Protocol

Each subject underwent a clinical polysomnogram (PSG) to measure OSA severity and a research PSG to measure the four OSA traits. For the clinical PSG, subjects were set up with the standard clinical montage that included electroencephalogram (EEG), electrooculogram, submental and leg electromyogram, electrocardiogram, nasal pressure and thermistor, respiratory effort (piezoelectric bands placed around the chest and abdomen), body position, and arterial oxygen saturation monitored at the finger. Subjects slept in the supine position for at least 4 h. All PSG data were collected and stored using the Alice digital PSG system (Philips Respironics, Murrysville, PA). A single sleep technician blinded to the subjects' ages was responsible for scoring sleep state, arousals, and respiratory events according to standard American Academy of Sleep Medicine (AASM) criteria.[19]

For the research PSG, subjects slept in the supine position with the same monitoring equipment as the clinical PSG. In addition, they were fitted with a sealed nasal mask (Gel Mask; Philips Respironics) attached to a pneumotachometer (model 3700A; Hans-Rudolph, Kansas City, MO) for measuring airflow. The mask was connected to a positive/negative pressure source (Pcrit 3000, Philips Respironics) to enable rapid switching between CPAP levels. The pressure in the mask was measured by a pressure transducer (Validyne, Northridge, CA) connected to a port in the mask. Carbon dioxide (CO_2) was continuously recorded from a catheter placed inside the nostril and measured with a capnograph (Vacumed, Ventura CA). All signals were sampled at 125 Hz and displayed using Nihon Kohden (Tokyo, Japan) and Spike 2 software (Cambridge Electronic Design Ltd, Cambridge, UK).

Measuring the Traits Responsible for OSA

All subjects were initially placed on a level of CPAP that abolished flow limitation and snoring, with flow limitation defined as a characteristic peak–plateau or obvious flattening in inspiratory airflow. The method for measuring the physiological traits uses 2- to 3-min CPAP decreases or drops, repeatedly performed to varying degrees of sub-therapeutic pressures during stable NREM (i.e., stages 2-4) sleep (Figure 1), to produce differing degrees of flow limitation.[8] The changes in ventilation that accompany the flow limitation are then used to calculate the four traits. The analysis of the data derived from the CPAP drop technique has been described in detail previously.[8] Briefly, all artefact-free CPAP drops were imported into MATLAB (Mathworks, Natick, MA) for analysis. Tidal volume, breath duration, and breath-by-breath minute ventilation were calculated using the leak-corrected flow signal. CPAP drops were included only from periods when the subject was in the supine position.

Resting Ventilation

Before every CPAP drop, each subject's resting minute ventilation (referred to as V_{eupnea}) was quantified as the mean ventilation 1 min prior to each CPAP drop.

Loop Gain, Delay, and the Time Constant

Loop gain (LG) is the ventilatory response to the disturbance ratio and is a measure of the sensitivity of the ventilatory control feedback loop. Figure 1 illustrates how LG can be measured from a CPAP drop. When CPAP is dropped, partial obstruction of the airway and a reduction in ventilation occur. Subsequently, carbon dioxide increases, which in turn increases ventilatory drive and stimulates upper airway muscle activation. The activation of these muscles can, in some patients, partially reopen the airway, and increase ventilation from the beginning of the CPAP drop to the end of the CPAP drop (defined by V_{uag} in Figure 1). Despite this partial recovery, ventilation often remains below the eupneic level despite the increased levels of ventilatory drive. The amount that ventilatory drive rises over the course of the drop can be determined by returning CPAP to the therapeutic level (thereby rapidly opening the airway) and measuring the overshoot in ventilation (V_r). The ratio of this ventilatory response (labeled V_r) to the reduction in ventilation (ventilatory disturbance or V_d) provides a measure of steady-state LG where $LG = -V_r/V_d$. For a CPAP drop to be used to calculate LG, minute ventilation had to be significantly reduced from the eupneic level for the last 60 sec of the CPAP drop and no arousals could occur during this interval. All drops that met the criteria were spliced (to include the last 60 sec of the drop and 3 min following return to the therapeutic level), then normalized and ensemble averaged to produce a mean ventilation trace. This ensemble-averaged trace was then input to

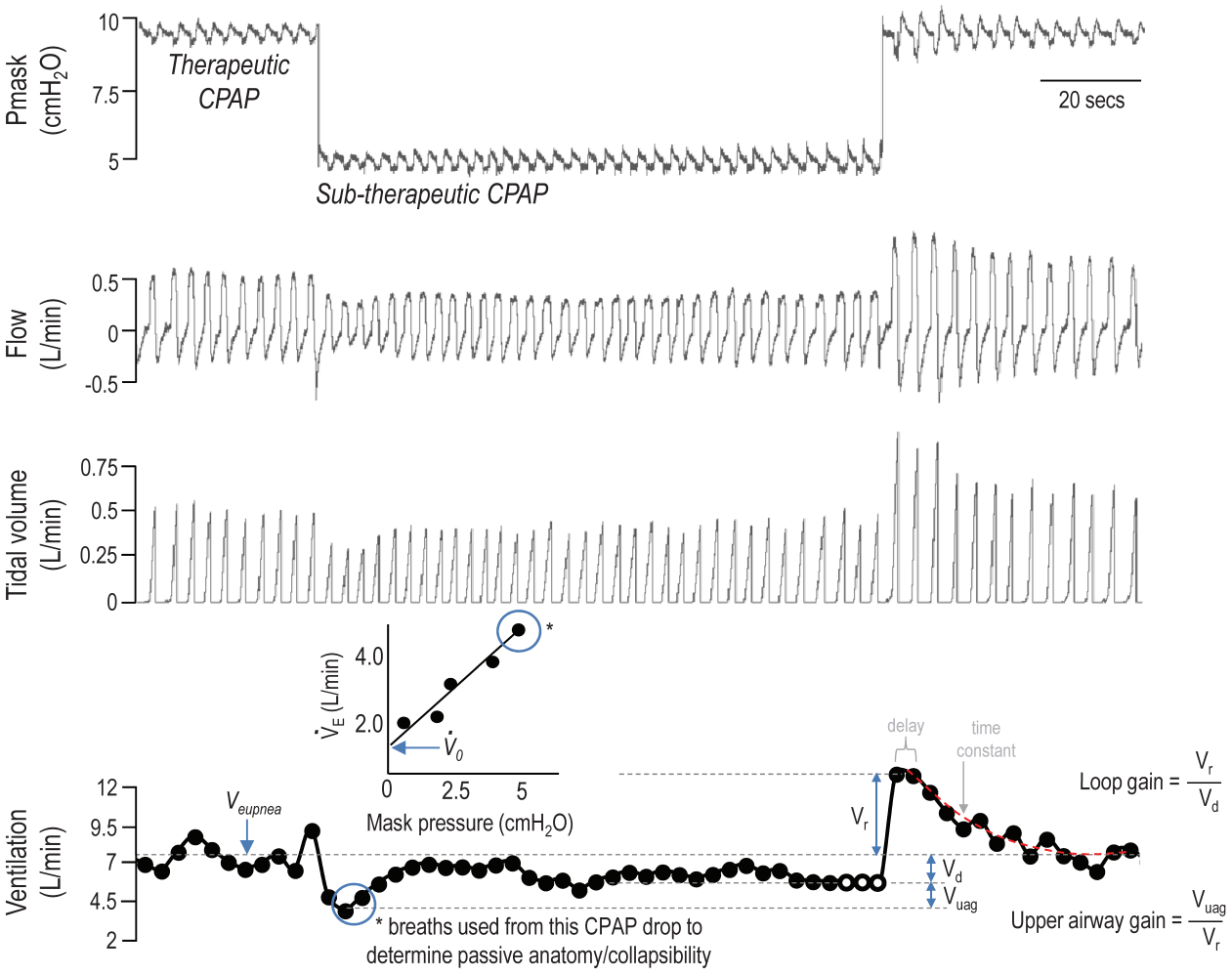

Figure 1—Technique for determining the physiological traits using continuous positive airway pressure (CPAP) drops. A representative example of a CPAP drop to demonstrate how all the changes in ventilation was used to assess the physiological traits. The top panel shows CPAP being dropped from the therapeutic level of 9 cmH_2O to a sub-therapeutic level of 3.5 cmH_2O. The effect that the CPAP reduction has on flow, tidal volume and minute ventilation is also shown. Resting ventilation (V_{eupnea}) is determined from the 60-sec average of ventilation preceding the CPAP drop. When CPAP is dropped there is an immediate reduction in flow (due to airway narrowing) that is reflected in the measured tidal volume and calculated minute ventilation. The reduction in ventilation leads to an increase in respiratory drive (labeled V_r). We measure how much ventilatory drive accumulates by rapidly restoring CPAP to the therapeutic level and measuring the overshoot in ventilation (V_r). The ratio of this ventilatory response or overshoot (V_r) to the net reduction in ventilation during the drop period (V_d) provides a measure of loop gain (V_r/V_d). A delay and time constant are also estimated from the dynamics of the ventilatory overshoot. In response to the increase in drive (V_r), the subject activates his or her upper airway muscles and partially reopens the airway, allowing for ventilation to recover slightly (V_{uag}: determined by subtracting the mean ventilation on the last three breaths [open circles] of the drop from the mean ventilation of breaths two and three of the drop [circled]). The ratio of the compensatory increase in ventilation (V_{uag}) to the increase in ventilatory drive (V_r) across the drop provides a measure of neuromuscular compensation (V_{uag}/V_r), which we refer to as the upper airway gain (UAG). The breaths (two to three) following the reduction in CPAP were used to calculate the pharyngeal collapsibility or (see text for details) – the inset shows how the breaths from the current drop [circled] are placed on a graph of ventilation vs. mask pressure in order to calculate. Finally, if an arousal occurs during a drop, we quantify the arousal threshold as the level of ventilatory drive immediately preceding the arousal. However, in the example shown, there was no EEG arousal and thus this drop could not be used to determine arousal threshold.

a well-established minimal model of the ventilatory control system,[20] to determine three characteristic parameters: the steady-state LG, the time constant of the ventilatory control system, and a delay (e.g., between the lungs and chemoreceptors). These parameters were identified for each subject using the System Identification Toolbox in MATLAB.

The components of steady-state LG, namely controller gain (ventilatory sensitivity to CO_2) and plant gain (change in end-tidal CO_2 for a given change in ventilation), were also determined as detailed previously.[21] Briefly, plant gain ($\Delta P_{ET}CO_2/\Delta \dot{V}_E$) was calculated based on the slope of the metabolic hyperbola and controller gain was subsequently deduced by dividing LG by plant gain (rearranging the equation; LG = controller × plant gain).

Upper Airway Gain/Responsiveness

The responsiveness of the upper airway muscles, referred to as the upper airway gain (UAG), was measured as the ratio of the amount that ventilation increases across the drop (V_{uag}) to the amount that ventilatory drive rises during the drop (V_r), and represents the ability of the airway to stiffen/dilate in response

to increases in ventilatory drive. In order to calculate the UAG, only CPAP drops in which no arousal occurred were used. V_{uag} was calculated by subtracting the mean ventilation on the last three breaths of the drop from the mean ventilation of breaths two and three of the drop. V_r was calculated by subtracting the mean ventilation of the first two breaths of the ventilatory overshoot (after CPAP was returned to the holding pressure) from the eupneic ventilation on optimum CPAP. The UAG is therefore = V_{uag}/V_r, where a positive value indicates compensation, i.e., increased ventilatory drive, leads to a partial recovery of ventilation. By contrast, values near zero or negative values (i.e., no change or a further reduction in ventilation despite increased drive) indicate an inability to compensate.

Table 1—Effect of age on anthropometric data

Variable	Young (n = 10)	Old (n = 10)
Age (y)	32.1 ± 1.8	64.7 ± 1.2 [a]
Sex (M/F)	8/2	7/3
Height (cm)	179.8 ± 3.9	169.3 ± 2.6 [a]
Weight (kg)	106.7 [99.0-113.0]	88.3 [77.5-105.3] [a]
BMI (kg/m^2)	34.9 ± 1.8	31.3 ± 2.0
CPAP requirement (cmH_2O)	11.4 ± 0.8	11.9 ± 1.1
CPAP compliance (h/night)	6.7 ± 0.4	6.6 ± 0

Values are means ± standard error of the mean. [a] Significant difference compared with the younger obstructive sleep apnea cohort. BMI, body mass index; CPAP, continuous positive airway pressure; F, female; M, male.

Table 2—Effect of aging on sleep disordered breathing

Variable	Young (n = 10)	Old (n = 10)
Total AHI (events/h)	48.8 ± 9.3	43.0 ± 6.2
Total sleep time (min)	315.5 ± 14.4	322.6 ± 15.5
REM duration (min)	33.0 ± 8.2	38.3 ± 7.3
NREM duration (min)	284.8 ± 11.6	284.7 ± 12.3
% Sleep efficiency (TST/TIB)	81.5 ± 3.8	74.4 ± 4.3
% REM (TST)	9.8 ± 2.4	11.5 ± 2.1
% Stage 1 (TST)	44.7 ± 8.5	47.4 ± 7.3
% Stage 2 (TST)	44.3 ± 6.6	40.9 ± 6.1
% Stage 3 (TST)	0 [0-1.0]	0 [0-0]
% Stage 4 (TST)	0 [0-0.2]	0 [0-0]
Mean overnight SaO_2 (%)	94.6 ± 0.5	94.7 ± 0.7
Lowest SaO_2 (%)	79.7 ± 2.5	81.0 ± 2.3
Oxygen desaturation index (events/h)	40.9 ± 9.6	40.7 ± 10.7
Total arousal index (events/h)	47.2 ± 9.3	36.3 ± 7.9
Respiratory arousal without desaturation (events/h)	4.1 ± 0.7	2.5 ± 0.8
Respiratory arousal with desaturation (events/h)	19.5 [5.8-53.2]	17.0 [11.5-25.5]
Leg movement arousals (events/h)	0 [0-0.1]	0 [0-0.9]
Spontaneous arousal index (events/h)	14.9 ± 2.9	12.6 ± 2.1
Leg movements (events/h)	0 [0-0.2]	0 [0-7.6]

Group data from the clinical polysomnogram in the supine posture and in the absence of continuous positive airway pressure. Values are means ± standard error of the mean or medians [interquartile range]. There was no statistical difference in any of the sleep measures between the young and old groups. AHI, apnea-hypopnea index; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; SaO_2, arterial blood oxygen saturation; TIB, time in bed; TST, total sleep time.

Passive Anatomy/Collapsibility

The passive anatomy, or pharyngeal collapsibility, was quantified by the ventilation on zero CPAP ($\dot{V}_0$) when the upper airway muscles are inactive or passive. $\dot{V}_0$ is determined by plotting mask pressure against ventilation for the third and fourth breaths of all CPAP drops throughout the night. These data points are then fit with a straight line (using linear regression) and $\dot{V}_0$ is the y-intercept. A high ventilation value on zero CPAP indicates a good anatomy (i.e. resistant to airway collapse), whereas a low number indicates a poor anatomy (i.e. highly collapsible airway), because the subject is not able to achieve much ventilation at zero CPAP.

Arousal Threshold

The arousal threshold was quantified as the ventilatory drive preceding arousal, defined as > 3 sec of an abrupt increase in EEG frequency. Using a dynamic model of the ventilatory control system, the observed changes in ventilation that occur during the CPAP drops were transformed into a ventilatory drive based on a transfer function model with a steady-state LG, time constant and delay (measured during the drops from which LG was estimated). A ventilatory drive signal was then calculated for every CPAP drop. Once ventilatory drive was known, the arousal threshold could be determined from those CPAP drops in which an arousal occurred (see supplemental material for additional details).

Statistical Analysis

Either independent samples *t*-tests or Mann–Whitney U tests were used to assess the effects of aging as appropriate and were performed using SigmaPlot (Systat Software, CA). $P \leq 0.05$ was considered significant. Values are presented as means ± standard error of the mean or median [interquartile range] as appropriate.

RESULTS

Subject demographics are shown in Table 1. By design, there was no difference in sex and BMI (despite younger individuals being both taller and heavier) between the groups. Both the objective CPAP compliance (average nightly usage over the past 30 days) and therapeutic CPAP requirement used were also similar between groups. There were no differences in major sleep characteristics between groups (Table 2) or respiratory event frequency during the clinical PSG (Table 3). However, the overall mean event duration was shorter in the younger subjects (26.8 ± 1.3 versus 32.6 ± 2.8 sec; $P < 0.05$), which was driven by shorter hypopnea durations in NREM (Table 3).

Effect of Aging on the OSA Traits

The four traits were estimated from 22.2 ± 1.4 and 21.3 ± 3.4 CPAP drops per subject per night in the younger and older

subjects, respectively. The percentage of drops that were used to estimate LG and UAG (i.e., drops that did not end prematurely in an arousal with awakening) were similar in the young (16.0 ± 3.5%) and old group (19.1 ± 3.5%). There was no difference in arousal duration (13.1 ± 1.3 versus 15.9 ± 2.4 sec; P = not significant [NS]) or time to arousal from the start of the drop (44.5 ± 8.8 versus 52.2 ± 10.2 sec; P = NS) between groups.

Compared to younger individuals with OSA, older patients had a decreased minute ventilation on therapeutic CPAP or V_{eupnea} (8.2 ± 0.5 versus 6.1 ± 0.4 L/min; P < 0.01), a lower steady-state LG (5.0 ± 0.7 versus 2.9 ± 0.5; P < 0.05, Figure 2A), and a shorter time constant (81.3 ± 16.4 versus 45.5 ± 5.0 sec; P = 0.05) but no difference in circulation delay (8.0 ± 1.8 versus 8.2 ± 1.5 sec). The lower LG was primarily driven by a lower controller gain (0.70 ± 0.11 versus 0.36 ± 0.06 L/min/mmHg; P < 0.05, Figure 2B), as plant gain (Figure 2C) was similar between groups (7.47 ± 0.49 versus 8.55 ± 0.63 mmHg/L/min). Linear regression using pooled data demonstrated that both LG and controller gain were modestly negatively correlated with NREM respiratory event duration (P < 0.05, Figure 3).

The effect of age on the remaining OSA traits is illustrated in Figure 4. $\dot{V}_0$ was significantly lower in the older subjects (3.4 ± 0.9 versus 1.5 ± 0.7 L/min; P = 0.05), indicating that the airway becomes significantly more collapsible with age, whereas UAG (P = 0.9) and the arousal threshold (P = 0.16) were similar across age groups.

Table 3—Effect of aging on NREM and REM sleep disordered breathing events and durations

	Index (events/h)		Event duration (sec)	
Sleep stage	**Young**	**Old**	**Young**	**Old**
NREM sleep				
Overall AHI	45.8 ± 9.4	40.8 ± 6.8	26.9 ± 1.4	33.1 ± 2.8 [a]
Central apneas	0 [0-0.3]	0.5 [0-1.4]	6.4 ± 2.7	16.1 ± 4.0
Obstructive apneas	1.3 [0-5.8]	0.9 [0.2-5.6]	14.9 ± 3.5	20.3 ± 4.0
Mixed apneas	0 [0-0.4]	0.1 [0-1.2]	0 [0-25.7]	8.8 [0-26.7]
Hypopneas	41.8 ± 8.8	35.8 ± 6.3	27.4 ± 1.4	33.9 ± 2.7 [a]
REM sleep				
Overall AHI	43.5 ± 10.1	37.4 ± 6.9	28.1 [22.5-31.8]	26.2 [23.2-32.6]
Central apneas	0 [0-1.0]	0 [0-0.2]	0 [0-11.5]	0 [0-4.3]
Obstructive apneas	0 [0-10.1]	1.7 [0-6.5]	0 [0-29.1]	17.4 [0-21.8]
Mixed apneas	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]
Hypopneas	35.1 ± 8.1	30.8 ± 6.2	31.3 [23.6-33.1]	27.8 [23.6-33.1]

Data represent medians [interquartile ranges] or means ± standard error of the mean. [a] Significant difference between young and old subjects with obstructive sleep apnea. AHI, apnea/hypopnea index; NREM, nonrapid eye movement; REM, rapid eye movement.

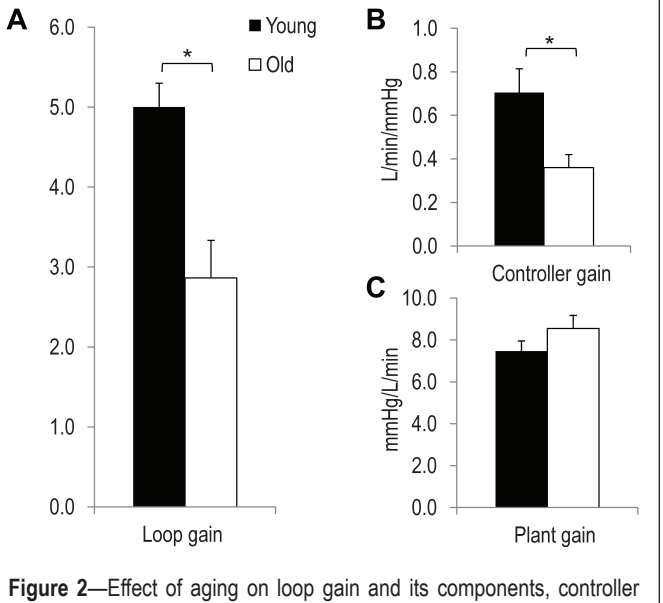

Figure 2—Effect of aging on loop gain and its components, controller and plant gain. The loop gain magnitude was approximately 50% (43% reduction) lower in the older subjects compared to the young subjects with OSA **(A)**. The reduction in loop gain was driven by reductions in controller gain **(B)** with aging, as plant gain **(C)** remained unchanged. *P < 0.05.

DISCUSSION

The major finding of our study was that among patients with OSA, the collapsibility of the pharyngeal airway worsens with aging, whereas the sensitivity of the ventilatory control system (i.e., LG) and the minute ventilation on therapeutic CPAP (i.e. V_{eupnea} or ventilatory demand) decreases. Our findings suggest that OSA in older adults is a unique phenotype due primarily to a worsening of the upper airway anatomy/collapsibility. This effect, however, is mitigated by a reduced ventilatory demand and feedback control sensitivity with age. By contrast, the phenotype in younger adults is one in which the airway is less collapsible, but a higher LG and greater ventilatory demand are dominant traits likely to contribute to the pathogenesis of OSA.

Changes in OSA Traits with Age

Anatomy/Collapsibility

In the current study, we found that the upper airway collapsibility ($\dot{V}_0$) was worse in the older group. This result is consistent with a previous study that demonstrated in a large cohort of patients with OSA that age, independent of sex and BMI, was a significant predictor of pharyngeal collapsibility.[22] Furthermore, worsening collapsibility is also found throughout life in healthy individuals, either when comparing children to adults,[12] or with increasing age in adulthood.[11] A number of studies suggest possible mechanisms for the age-related increase in pharyngeal collapsibility. Martin et al.[23] measured upper airway caliber using acoustic reflection and found that all upper airway dimensions, except at the oropharyngeal junction, decreased modestly with age. Reduced airway caliber may be caused by the increased deposition of parapharyngeal fat in older individuals in comparison with younger control patients, a finding that was independent of BMI.[15] Overnight fluid shift from the periphery into the trunk and neck has also been identified as a factor that

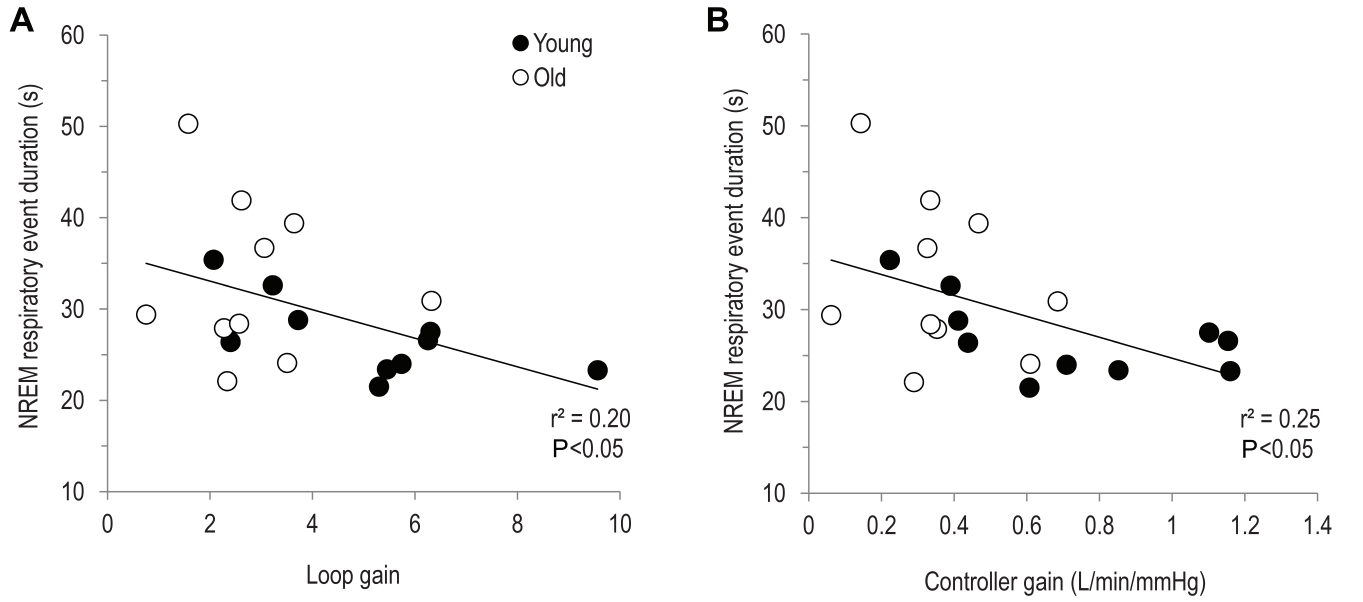

Figure 3—Relationship between respiratory event length and respiratory control indices. Pooling the average respiratory event duration data from all young (black circles) and old (white circles) subjects, we found that loop gain magnitude **(A)** was inversely associated with NREM respiratory event duration (i.e., the lower the loop gain magnitude the longer the respiratory event), a relationship driven by controller gain **(B)**.

may reduce the caliber of the upper airway and thus increase its propensity toward collapse. A recent study in nonobese individuals with OSA demonstrated that age was positively correlated with the amount of fluid shifting rostrally overnight.[24] The authors argued that this finding may be caused by a more sedentary lifestyle in older adults, which can contribute to a greater amount of fluid accumulation in the legs during the day. The effect of age on other factors that increase pharyngeal collapsibility, such as increases in surface tension of the upper airway[25] or decreases in lung volume tethering effects,[26] may also be important and thus warrant investigation.

Loop Gain

Given the observations that aging is associated with an increased number of central apneas,[27] oscillatory breathing,[28] and with Cheyne-Stokes respiration in those with heart failure,[29] we suspected that the ventilatory control system may become more sensitive with age. In fact, the current work shows that the steady-state LG decreases with aging in individuals with OSA. The longer respiratory events observed in older patients with OSA[30] are also consistent with a less sensitive control system; indeed, our data confirm that the increase in event duration is associated with the decrease in LG with aging. Furthermore, a lowered LG with age is consistent with data in healthy subjects[13]; this relationship is likely driven by the known reduction in the ventilatory sensitivities to both oxygen and carbon dioxide with age.[31] The current study confirms this finding by demonstrating that the aging-induced reduction in LG is driven solely via the decreases in controller gain, as plant gain was not different between groups. Overall, the available evidence suggests that the aging process leads to desensitization of the ventilatory control system.

Upper Airway Responsiveness

There is some evidence to suggest that aging attenuates the response of the genioglossus muscle (a major pharyngeal dilator muscle) to pharyngeal negative pressure stimuli[15] and hypoxia[32]; however, these studies were conducted in healthy subjects during wakefulness. Thus, we do not know if (1) these deficits carry over into sleep, (2) are relevant in patients with OSA, and (3) whether reduced muscle responses that occur with aging translate into impairments in airflow. Interestingly, Patil et al.[33] found no age-related change in the dynamic responses to upper airway obstruction (sometimes referred to as active P_{crit}) during sleep in patients with OSA, a finding analogous to our observation that UAG was not altered with age.

Arousal Threshold

As several studies in older individuals have shown an increased number of spontaneous arousals during sleep,[14] older adults might be expected to have a lower arousal threshold compared to younger individuals. In the current study we found no difference in the arousal threshold with age, a finding that is consistent with a cohort of healthy subjects,[11] even when matched for BMI. Thus, the available data suggest that any effect that aging has on the arousal threshold appears negligible.

Are the Physiological Causes of OSA Different in Older Adults?

A major strength of the current work is that four physiological traits known to contribute to OSA were assessed simultaneously. To provide a detailed assessment of whether OSA might be caused by different mechanisms (or their interactions) in older compared to young individuals, we input the mean measurements of each trait into our previously published model (Figure 5).[8] Ventilatory drive is represented on the x-axis and ventilation on the y-axis. The black circle represents the resting ventilation (V_{eupnea}) on therapeutic CPAP (e.g., 8.2 L/min for young subjects; panel A), which is equal to resting ventilatory drive (i.e., when the airway is fully patent). The slope of the black solid line is the reciprocal of the calculated LG, which shows how ventilatory drive increases as ventilation is reduced.

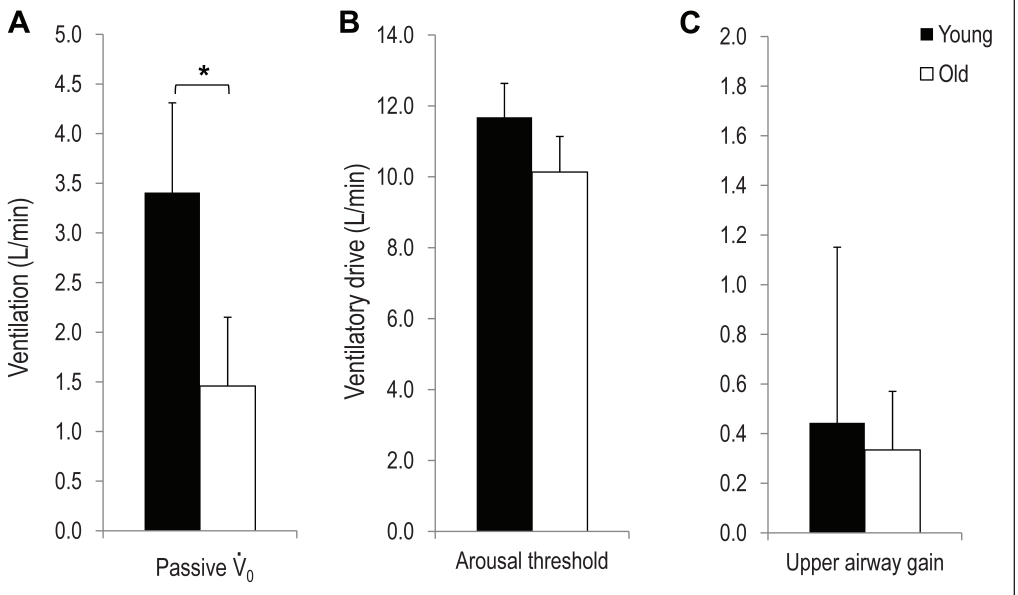

Figure 4—Effect of aging on the other pathophysiological obstructive sleep apnea traits. Aging was associated with a worsening of the passive airway collapsibility as measured by $\dot{V}_0$ **(A)**; however, there was no difference in the arousal threshold **(B)** or the upper airway gain **(C)** between the two groups. *P = 0.05.

The gray dot represents the ventilation off CPAP at the eupneic ventilatory drive ($\dot{V}_0$), and the slope of the gray solid line indicates how ventilation responds to increasing ventilatory drive (i.e., UAG). The point of intersection between the LG and UAG lines is the predicted steady-state ventilation off CPAP when ventilatory drive has increased. The gray dashed line represents the ventilatory drive threshold that when reached causes an arousal from sleep (i.e., arousal threshold). If the predicted steady-state ventilation off CPAP is to the left of the arousal threshold, then the model predicts that breathing would remain stable (i.e., no OSA) because a mutually agreeable ventilation and ventilatory drive have been achieved at a ventilatory drive that is below the arousal threshold. However, if the steady-state point lands to the right of the arousal threshold line, then arousal occurs before stable breathing can be achieved as described below.

Figure 5A demonstrates that young subjects asleep on CPAP have a high resting ventilatory drive or V_{eupnea}. When CPAP is removed, the airway partially collapses and ventilation falls to 3.4 L/min. However, their passive anatomy would be considered quite good based on similarity to previous data in healthy subjects (mean [± standard deviation] $\dot{V}_0$ in three control subjects = 3.0 ± 1.7 L/min, data from Wellman et al.[8]). As ventilation and ventilatory drive increase in response to this partial airway collapse in an effort to reach the intersection with the LG line, subjects hit their arousal threshold and arouse from sleep. As they fall asleep again, the airway partially collapses and the cycle repeats. Figure 5A suggests that a high resting ventilatory drive and high LG (relative to older adults) play a contributing role in the pathogenesis of OSA in young adults. If young subjects were to have a V_{eupnea} and LG similar to older adults, then the model would predict that the intersection of the LG and UAG line would occur in the stable region and they would not have OSA (Figure 5C). It follows that if both V_{eupnea} and LG were the only factors that declined with age, then this effect should be protective against the predisposition to develop OSA. By contrast, we found that the passive anatomy worsens with age and we propose this is the predominant reason why older individuals develop OSA (Figure 5B). If older individuals had a passive anatomy that was similar to younger individuals, then we would predict that they would be less likely to develop OSA (Figure 5D). Thus, our evidence suggests that young and old people have OSA for different reasons.

The concept that OSA is a different phenotype in older adults has also been suggested by studies that have shown strong associations between OSA and cardiovascular sequelae[34] or neurocognitive impairment[35] and sleepiness[36] in middle-aged populations but not in older individuals. The milder clinical impact of OSA in older adults may be because of smaller ventilatory and cardiovascular responses to respiratory events/arousals compared to younger individuals.[37] For example, older individuals who have been shown to produce less negative esophageal pressure during respiratory events than younger individuals may have reduced cardiac wall stress/tension (reflecting lower transmural pressure).[30] If the characteristics of this older OSA phenotype is not simply a survivor effect (discussed in Limitations), then we speculate that it may contribute to the attenuated cardiovascular and neurocognitive sequelae in older adults, thus supporting the concept of redefining OSA based on underlying mechanism rather than simply focusing on AHI.

Role of Ventilatory Demand (V_{eupnea}) in the Pathogenesis of OSA

Ventilatory demand (V_{eupnea}) is not typically considered a physiological trait; however, the current study illustrates that lowering V_{eupnea} is one possible way to achieve stable breathing and resolve OSA (Figure 5C). Theoretically, lowering V_{eupnea} by 1 L/min has the same effect as improving the passive anatomy ($\dot{V}_0$) by 1 L/min. That is, if a patient can only achieve a maximum ventilation of 5 L/min (see intersection of UAG and arousal threshold lines in Figure 5A) without arousing from sleep, then lowering V_{eupnea} to this level provides the possibility of stable breathing. V_{eupnea} can be lowered by either reducing metabolic rate or altering the characteristics of the ventilatory controller (i.e., reducing the slope of the ventilatory response to carbon dioxide or shifting this curve to the right). Our data suggest that the reduced V_{eupnea} observed in the older group is due to the combined effect of (1) reduced chemosensitivity (controller gain) and (2) a lowered metabolic production of carbon dioxide (compare 277 ± 24 versus 169 ± 16 mL/min; $P < 0.01$), which remained significantly different when accounting for differences in height and weight between age groups. Clearly more

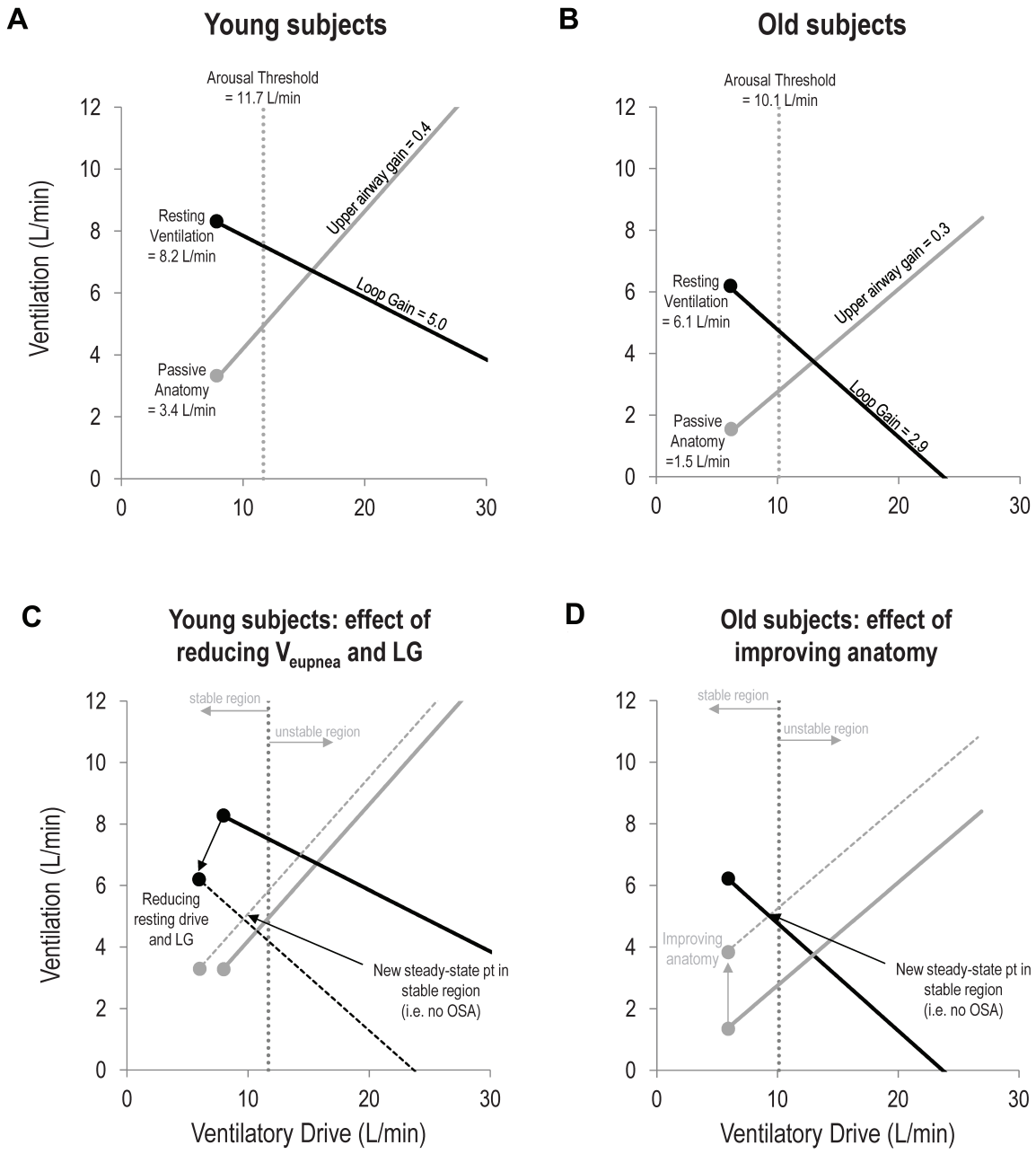

Figure 5—Differences in obstructive sleep apnea (OSA) pathogenesis between young and old subjects. Mean data of resting ventilation and the four physiological traits in young **(A)** and older subjects **(B)**. Aging significantly reduced resting ventilation ($P < 0.05$) and the passive anatomy or $\dot{V}_0$ ($P = 0.05$) by approximately 2 L/min during stable NREM sleep. Loop gain (LG) was reduced with age ($P < 0.05$); however, the arousal threshold and the upper airway gain remained unchanged. Note that both young subjects and older subjects have OSA for different reasons: young people primarily have a disorder of high ventilatory drive and LG, whereas in older individuals OSA primarily occurs due to a poor upper airway anatomy/collapsibility. If young people had a ventilatory drive and LG similar to older adults, our model predicts that the new steady-state ventilation (i.e., where the LG line and upper airway response line intersect) would lie in the stable region (i.e., to the left of the arousal threshold line) and that they would not have OSA **(C)**. Similarly, if older adults improved their poor passive anatomy, our model would also predict OSA resolution **(D)**.

evidence is needed to confirm the role that V_{eupnea} plays in the pathogenesis of OSA, but if V_{eupnea} can be considered as a fifth trait, then we now have another potential therapeutic target to treat OSA.

Limitations

In addition to the possible limitations associated with our technique,[8] there are several limitations that need to be considered when interpreting our findings. First, the small sample size in the current study may have meant that some of our comparisons were underpowered. Based on the results from the current study, we would need to study 70 young and 70 old subjects to determine definitively whether there was a reduced arousal threshold with age—which suggests that the true difference, if real, is small. Such a large study is clearly difficult to achieve in an intensive physiology laboratory.

Second, the cross-sectional nature of our study limits our ability draw firm conclusions as to whether the phenotypes are likely to change over time, or if the observed age-related differences were related to a selection bias. For example, it is plausible that the younger patients with OSA may not survive long enough to become old patients, and that the older group examined in the current study represents a specific survivor cohort in which their phenotype was protective; thus, it may not reflect an aging phenomenon *per se* as the older group may have had the same phenotype when they were younger. Third, it is possible that differences in the duration of exposure to CPAP (i.e., how long patients had been using CPAP) may have influenced our measurements of the four traits. Although we did not document the treatment duration in our study, studies that have assessed the effect of CPAP treatment on the phenotype traits have shown that 1 mo of CPAP therapy reduced controller gain (and therefore loop gain) back to the same levels measured in healthy controls,[18] and lowered the arousal threshold but did not alter the upper airway muscle responsiveness.[17] Such findings suggest that 1 mo of effective treatment is sufficient to reverse the consequences of disease and allows an individual's intrinsic physiology to be assessed. Given that our patients had at least 2 mo of documented CPAP usage, and that the average nightly usage (over the past 30 days) was not different between groups, we believe that any difference in duration of CPAP exposure between the groups is unlikely to affect our measurements (i.e., we are comparing the intrinsic physiology in both groups). Last, we did not study any subjects without OSA, making it difficult to demonstrate conclusively that the changes in the traits are caused by age alone. However, our reported changes in the traits in patients with OSA are consistent with existing data in healthy subjects. Nonetheless, until many of these limitations are addressed, we will not have the complete answer as to how the phenotypic traits are altered with age. Ultimately our findings need to be repeated in larger (ideally longitudinal) studies involving both patients with OSA (treated and untreated) and those without OSA.

CONCLUSIONS

Our data support the emerging concept that OSA may be a different phenotype in young versus old individuals. Young individuals with OSA have relatively good anatomy, but a higher respiratory drive and higher loop gain (LG) predispose them to OSA. Although the reduction in ventilatory drive and LG with age should protect against OSA, any reduction in the predisposition toward OSA is offset by worsening anatomy with age. Future research should focus on measuring physiological traits in large cohorts of subjects (ideally followed longitudinally) to assess definitively how aging alters the factors causing OSA and its sequelae.

ACKNOWLEDGMENTS

The authors would like to thank Ms. Lauren Hess and Mr. Erik Smales for their laboratory assistance. This work was supported by the National Institutes of Health: 5R01HL048531-16, R01 HL085188-02, R01 HL090897-01A2, K24 HL 093218-01A1, and P01 HL 095491, the American Heart Association: 0840159N, 0575028N, and the Harvard Catalyst Clinical Research Center: UL1 RR 025758-01. During the collection of the data, Dr. Edwards was supported by the Thoracic Society of Australia and New Zealand/Allen and Hanbury's Respiratory Research Fellowship. Dr. Edwards is currently supported by the National Health and Medical Research Council (NHMRC) of Australia's CJ Martin Overseas Biomedical Fellowship (1035115). Dr. Sands was supported by an American Heart Association fellowship (11POST7360012) and is currently supported by NHMRC Early Career Fellowship (1053201) and R.G. Menzies award. Dr. Eckert was supported by the American Heart Association (10SDG3510018), an NHMRC of Australia Overseas Biomedical Fellowship (510392), and is currently supported by a NHMRC R.D. Wright Fellowship (1049814).

DISCLOSURE STATEMENT

This was not an industry-sponsored study. Dr. Wellman is a consultant for Philips Respironics, SOVA Pharmaceuticals and Apnex Medical. Dr. Owens consults for Apnex Medical, Apnicure and Philips Respironics. Dr. White was the chief medical officer for Philips Respironics until 12/31/12 but is now the chief scientific officer for Apnicure Inc as of January 2013. Dr. Malhotra was a consultant for Philips Respironics, SHC, SGS, Apnex Medical, Pfizer, Apnicure, but has relinquished all outside personal income since May 2012. The other authors have indicated no financial conflicts of interest.

REFERENCES

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–5.
2. Roth T, Roehrs T, Rosenthal L. Hypersomnolence and neurocognitive performance in sleep apnea. Curr Opin Pulm Med 1995;1:488–90.
3. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378–84.
4. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001;163:19–25.
5. Young T, Shahar E, Nieto FJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med 2002;162:893–900.
6. Mehra R, Stone KL, Varosy PD, et al. Nocturnal Arrhythmias across a spectrum of obstructive and central sleep-disordered breathing in older men: outcomes of sleep disorders in older men (MrOS sleep) study. Arch Intern Med 2009;169:1147–55.
7. Ancoli-Israel S, Kripke DF, Klauber MR, et al. Morbidity, mortality and sleep-disordered breathing in community dwelling elderly. Sleep 1996;19:277–82.
8. Wellman A, Eckert DJ, Jordan AS, et al. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. J Appl Physiol 2011;110:1627–37.
9. Wellman A, Edwards BA, Sands SA, et al. A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. J Appl Physiol 2013;114:911–22.
10. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am J Respir Crit Care Med 2013;188:996–1004.
11. Eikermann M, Jordan AS, Chamberlin NL, et al. The influence of aging on pharyngeal collapsibility during sleep. Chest 2007;131:1702–9.
12. Marcus CL, Lutz J, Hamer A, Smith PL, Schwartz A. Developmental changes in response to subatmospheric pressure loading of the upper airway. J Appl Physiol 1999;87:626–33.
13. Wellman A, Malhotra A, Jordan AS, Schory K, Gautam S, White DP. Chemical control stability in the elderly. J Physiol 2007;581:291–8.
14. Redline S, Kirchner HL, Quan SF, Gottlieb DJ, Kapur V, Newman A. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. Arch Intern Med 2004;164:406–18.

15. Malhotra A, Huang Y, Fogel R, et al. Aging influences on pharyngeal anatomy and physiology: the predisposition to pharyngeal collapse. Am J Med 2006;119:72 e9–14.
16. Edwards BA, Sands SA, Eckert DJ, White DP, Malhotra A, Wellman A. Changes in ventilatory control sensitivity with ageing in patients with obstructive sleep apnea. Respirology 2012;17(Suppl 1):27.
17. Loewen A, Ostrowski M, Laprairie J, et al. Determinants of ventilatory instability in obstructive sleep apnea: inherent or acquired? Sleep 2009;32:1355–65.
18. Salloum A, Rowley JA, Mateika JH, Chowdhuri S, Omran Q, Badr MS. Increased propensity for central apnea in patients with obstructive sleep apnea: effect of nCPAP. Am J Respir Crit Care Med 2009:200810–1658OC.
19. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667–89.
20. Khoo MC. Physiological control systems. Analysis, simulation and estimation. New York: IEEE Press, 2000.
21. Edwards BA, Sands SA, Eckert DJ, et al. Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. J Physiol 2012;590:1199–211.
22. Kirkness JP, Schwartz AR, Schneider H, et al. Contribution of male sex, age, and obesity to mechanical instability of the upper airway during sleep. J Appl Physiol 2008;104:1618–24.
23. Martin SE, Mathur R, Marshall I, Douglas NJ. The effect of age, sex, obesity and posture on upper airway size. Eur Respir J 1997;10:2087–90.
24. Redolfi S, Yumino D, Ruttanaumpawan P, et al. Relationship between overnight rostral fluid shift and Obstructive Sleep Apnea in nonobese men. Am J Respir Crit Care Med 2009;179:241–6.
25. Kirkness JP, Madronio M, Stavrinou R, Wheatley JR, Amis TC. Relationship between surface tension of upper airway lining liquid and upper airway collapsibility during sleep in obstructive sleep apnea hypopnea syndrome. J Appl Physiol 2003;95:1761–6.
26. Heinzer RC, Stanchina ML, Malhotra A, et al. Effect of increased lung volume on sleep disordered breathing in patients with sleep apnoea. Thorax 2006;61:435–9.
27. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med 1998;157:144–8.
28. Hudgel DW, Devadatta P, Hamilton H. Pattern of breathing and upper airway mechanics during wakefulness and sleep in healthy elderly humans. J Appl Physiol 1993;74:2198–204.
29. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 1999;160:1101–6.
30. Kobayashi M, Namba K, Tsuiki S, Matsuo A, Sugiura T, Inoue Y. Clinical characteristics in two subgroups of obstructive sleep apnea syndrome in the elderly: comparison between cases with elderly and middle-age onset. Chest 2010;137:1310–5.
31. Kronenberg RS, Drage CW. Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal men. J Clin Invest 1973;52:1812–9.
32. Klawe JJ, Tafil-Klawe M. Age-related response of the genioglossus muscle EMG-activity to hypoxia in humans. J Physiol Pharmacol 2003;54:14–9.
33. Patil SP, Schneider H, Marx JJ, Gladmon E, Schwartz AR, Smith PL. Neuromechanical control of upper airway patency during sleep. J Appl Physiol 2007;102:547–56.
34. Haas DC, Foster GL, Nieto FJ, et al. Age-dependent associations between sleep-disordered breathing and hypertension: importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the Sleep Heart Health Study. Circulation 2005;111:614–21.
35. Foley DJ, Masaki K, White L, Larkin EK, Monjan A, Redline S. Sleep-disordered breathing and cognitive impairment in elderly Japanese-American men. Sleep 2003;26:596–9.
36. Morrell M, Finn L, McMillian A, Peppard PE. The impact of aging and gender on the association between sleepiness and sleep disordered breathing. Eur Respir J 2012;40:386–93.
37. Goff EA, O'Driscoll DM, Simonds AK, Trinder J, Morrell MJ. The cardiovascular response to arousal from sleep decreases with age in healthy adults. Sleep 2008;31:1009–17.

SUPPLEMENTAL METHODS AND RESULTS

Measuring the Passive Anatomy/Collapsibility: Comparison with P_{crit}

The passive anatomy or pharyngeal collapsibility was quantified by the ventilation on zero CPAP ($\dot{V}_0$) when the upper airway muscles are inactive or passive. $\dot{V}_0$ is determined by plotting mask pressure against ventilation for the second and third breaths of all CPAP drops throughout the night. These data points are then fit with a straight line (using linear regression) and $\dot{V}_0$ is the y-intercept. A high ventilation value on zero CPAP indicates a good anatomy (i.e. resistant to airway collapse), whereas a low number indicates a poor anatomy (i.e. a highly collapsible airway), as the subject is not able to achieve much ventilation at zero CPAP. It is worth noting that this technique is analogous to measuring the 'passive' critical pharyngeal closing pressure (P_{crit}), which plots peak flow (instead of ventilation) from the third through fifth flow-limited breaths after a pressure drop against mask pressure and fits these points with a straight line. The x-intercept of this line (zero flow crossing) is then taken as the P_{crit}.[1,2] From our CPAP drops we were also able to determine a P_{crit} for each subject. Similar to our analysis using , we found that the P_{crit} was less collapsible in the younger group (compare -1.0 ± 1.5 versus 0.8 ± 0.8 cmH_2O) and that P_{crit} and $\dot{V}_0$ were strongly correlated ($r^2 = 0.60$, $P < 0.001$).

Measuring the Arousal Threshold

The arousal threshold was quantified as the ventilatory drive preceding arousal, defined as >3 sec of an abrupt increase in electroencephalographic frequency. Using a dynamic model of the ventilatory control system, the observed changes in ventilation that occur during the CPAP drops were transformed into a ventilatory drive based on a transfer function model with a steady-state LG, time constant, and delay (measured during the drops from which LG was estimated). A ventilatory drive signal is then calculated for every CPAP drop. When ventilatory drive is known, the arousal threshold can be determined from those CPAP drops in which an arousal occurred. A schematic of how the arousal threshold is calculated is shown in Figure S1.

REFERENCES

1. Schwartz AR, Smith PL, Wise RA, Bankman I, Permutt S. Effect of positive nasal pressure on upper airway pressure-flow relationships. J Appl Physiol 1989;66:1626–34.
2. Smith PL, Wise RA, Gold AR, Schwartz AR, Permutt S. Upper airway pressure-flow relationships in obstructive sleep apnea. J Appl Physiol 1988;64:789–95.
3. Wellman A, Eckert DJ, Jordan AS, Edwards BA, Passaglia CL, Jackson AC, et al. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. J Appl Physiol. 2011;110:1627–37.

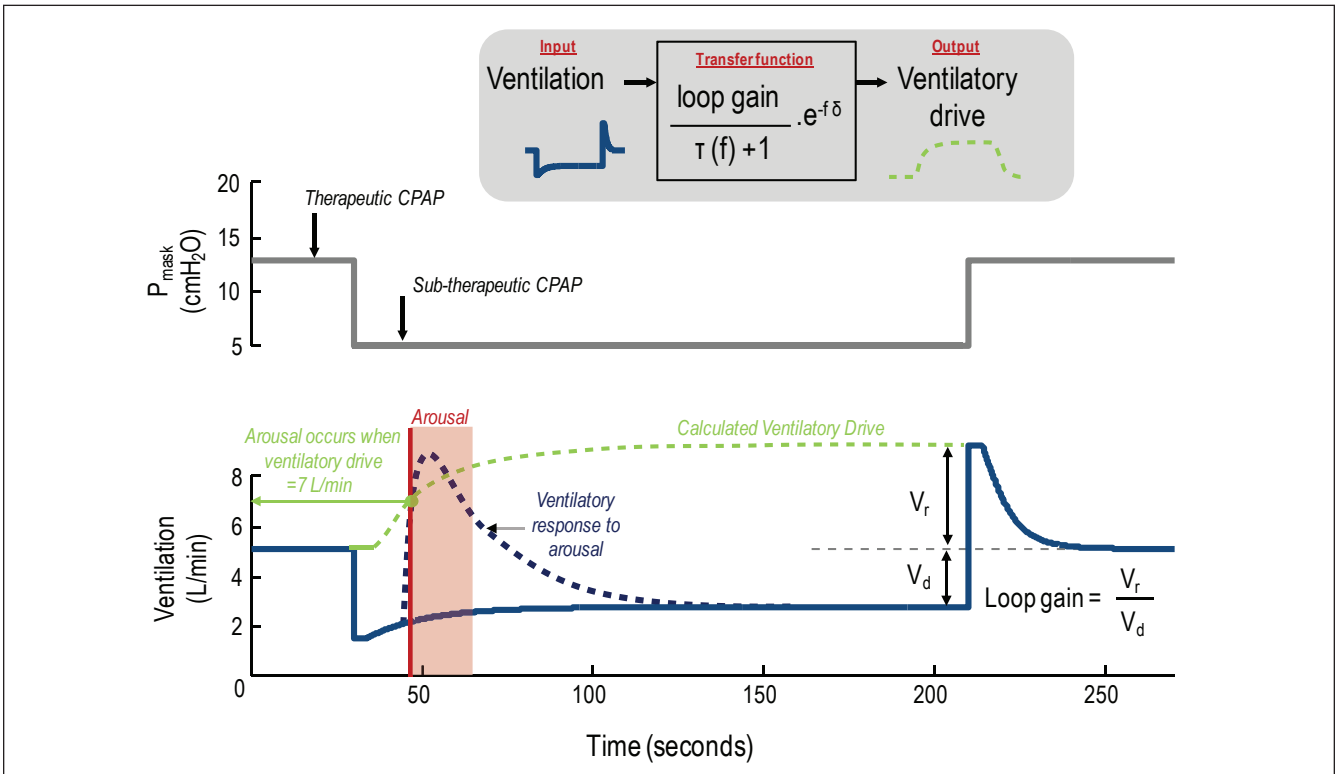

Figure S1—Technique for determining the arousal threshold using continuous positive airway pressure (CPAP) drops. After the loop gain (V_r/V_d), delay (δ), and time constant (τ) have been calculated from the CPAP drop, we can input the ventilation trace from each CPAP drop into a transfer function model, which uses the three parameters to output how ventilatory drive (dashed green line) will change as a result of the reductions in ventilation that have occurred during the drop. In this example, if an arousal was to occur soon after the CPAP was dropped (shaded area), the arousal threshold is quantified as the ventilatory drive preceding the arousal (7 L/min in this example). More details can be found in our previous publication.[3]