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## Aging and Sleep: Physiology and Pathophysiology

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### Abstract

Aging effects on sleep are important to consider for the practicing pulmonologist due to the increase in prevalence of major respiratory disorders as well as the normal changes that occur in sleep patterns with aging. Typically, aging is associated with decreases in the amount of slow wave sleep and increases in stage 1 and 2 non-rapid eye movement sleep, often attributed to an increased number of spontaneous arousals that occur in the elderly. Elderly individuals tend to go to sleep earlier in the evening and wake earlier due to a phase advance in their normal circadian sleep cycle. Furthermore the development of sleep-related respiratory disorders such as obstructive sleep apnea (OSA) and central sleep apnea or Cheyne-Stokes respiration (CSA-CSR) associated with congestive heart failure (CHF) occur with increasing prevalence in the elderly. The development of such disorders is often of major concern because they are associated with systemic hypertension and cardiovascular disease, metabolic disorders such as diabetes, and impaired neurocognition. The present review reflects the current understanding of the normal changes in sleep patterns and sleep needs with advancing age, in addition to the effect that aging has on the predisposition to and consequences of OSA and CSA-CSR associated with CHF.

### Keywords

Aging; sleep patterns; sleep apnea; congestive heart failure

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Sleep is a vital physiological process with important restorative functions that are essential for optimal day-time functioning. Insufficient or poor quality sleep has been associated with neurocognitive impairments,<sup>1,2</sup> end-organ dysfunction and chronic health conditions,<sup>3–5</sup> and increased mortality.<sup>6–8</sup> Importantly, aging is associated with both qualitative and quantitative changes in our sleep pattern and distribution. For instance, in infancy, sleep duration is at a lifetime maximum, with newborn infants sleeping for ~16 hours each day. This sleep requirement decreases through childhood, reaching 7 to 8 hours in adulthood. Although less well studied, there is evidence that sleep duration further decreases from young adulthood into our older years. However, such an idea remains controversial, with other studies suggesting that the amount of sleep does not change; instead sleep in the elderly becomes more fragmented and is usually consolidated through daytime naps. To

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date, several factors, such as cumulative health problems and changes in circadian influences have been hypothesized as mechanisms underlying reduced sleep quality in the elderly. In addition, a major factor contributing to poor-quality sleep is the presence of sleep-related disorders, which occur with increasing frequency among elderly people.<sup>9–11</sup>

The study of aging in the sleep field has been challenging for several reasons, many of which are true for aging research in general. First, the prevalence of comorbidities is high in the elderly, leading to discussion about what is normal aging. On the one hand, some would argue to exclude comorbidities and study the healthy elderly. On the other hand, some argue that these “super-healthy” individuals are not a representative or generalizable sample. Thus an ongoing debate exists regarding the definition of the term *healthy aging*. Second, some sleep research protocols can be somewhat onerous, and the ability to make careful assessments in vulnerable populations can be compromised. Thus the number of sleep papers focused on elderly cohorts is somewhat modest. Third, clinical samples reflect referral biases that are complicated in the field of sleep and aging. For example, the elderly may be less prone to sleepiness from sleep deprivation or sleep apnea; thus one could argue that they may be less likely to be referred with a clinical complaint. Similarly, the elderly may be more isolated than younger cohorts, and fewer bed partners and family members may be in a position to recognize a potential abnormality during sleep. In this article we review the existing literature in the context of our clinical and research experience. We review the current understanding aging’s impact on sleep as well as the pathogenesis and consequences of sleep-related disorders, namely obstructive sleep apnea (OSA) and central sleep apnea or Cheyne-Stokes respiration (CSA-CSR), including its association with congestive heart failure (CHF).

## PHYSIOLOGICAL CHANGES IN SLEEP PATTERNS WITH AGE

Accurate monitoring of sleep via polysomnography involves recording of cortical activity from the electroencephalogram (EEG), as well as recording of eye movements, muscle tone, and cardiorespiratory activity. Sleep is characterized by both non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep is further subdivided into three stages; N1 (formerly stage 1), N2 (stage 2), and N3 (stages 3 and 4) corresponding to increasing depth of sleep and differentiated by a specific electroencephalographic (EEG) frequency (Fig. 1, top panel). The transition from wakefulness to NREM sleep is associated with a reduction in ventilation and heart rate as well as a small reduction in metabolic rate, possibly due to relative autonomic stability. In contrast, during REM sleep ventilation becomes highly variable, and cardiovascular activity becomes irregular due to bursts of sympathetic nerve activity unique to REM sleep.

The distribution of sleep stages across the night, commonly referred to as sleep architecture, is displayed via a hypnogram (Fig. 1, bottom panel). In healthy adults, sleep progresses through NREM stages N1 through N3 followed by a period of REM occurring ~90 minutes into sleep. This sleep state cycling is a fundamental feature of sleep, although there is a reduction in N3 and increase in REM sleep as the night progresses. Sleep is punctuated by brief arousals (defined as an increase in EEG frequency to >8 Hz lasting longer than 3 seconds) and awakenings (periods of wakefulness >30 seconds). As we age, however, important changes in the patterns or structure of sleep occur, which have been the topic of several excellent reviews<sup>12–14</sup> that are summarized in Table 1 and illustrated in Fig. 1B. A meta-analysis of 65 studies representing 3577 healthy subjects has shown that the total amount of sleep decreases linearly with age with a loss of ~10 minutes per decade.<sup>15</sup> Sleep architecture also changes with age. Up to the age of 60 years, the percentage of N3 sleep decreases linearly at 2% per decade. The percentage of REM sleep also diminishes, although the decline is more subtle. As with N3, the percentage of REM sleep appears to plateau after

age 60. The net result of these changes is an increase in N1 and N2. In addition, sleep efficiency continues to decline due to increased sleep latency, arousals from sleep and time awake after sleep onset; however, the mechanisms responsible for these changes in sleep architecture are unclear. Although it has been postulated that these changes reflect age-related reduction in EEG amplitude produced by the increase in electrical impedance of the skull and scalp, they are more likely a reflection of age-related neural degeneration and changes in hormonal systems.<sup>16</sup>

Numerous studies have also identified an interesting gender disparity in these age-related changes in sleep architecture. Although many of these individual studies give conflicting results, a meta-analysis of 65 studies of healthy adults indicates that men are more affected by aging than women. In this analysis, men were shown to have decreased total sleep time, decreased percentage of N3 and REM sleep, and increased percentage of N2 and wake time after sleep onset compared with women.<sup>15</sup> On the other hand women had increased sleep latencies when compared with men. These findings are of particular interest given that women often self-report shorter and poorer sleep compared with men.<sup>17</sup> This greater perception of sleep difficulty in women is cited as the reason why women use hypnotics at a greater frequency than men.<sup>18</sup> The results of this meta-analysis on gender differences in age-related changes in sleep architecture were confirmed the same year with data from the Sleep Heart Health Study ( $n = 2685$ ).<sup>11</sup> Overall, whether this gender difference in sleep architecture is a result of hormonal changes or environmental factors remains to be elucidated.

In addition to the global changes that occur in the sleep architecture, several studies have examined the changes that occur in the microstructure of sleep. Such studies have demonstrated an age-related decrease in both spontaneous K-complexes and sleep spindle densities,<sup>19,20</sup> as well as the number and amplitude of evoked K-complexes.<sup>21</sup> The findings of these studies have been interpreted to reflect an age-related alteration of thalamocortical regulatory mechanisms, which could be used to identify the changes in neurobiology of the brain with advancing age.

Whether sleep *need* changes with aging is a more complex question; the relevant literature having been reviewed by Bliwise.<sup>14</sup> A large number of investigations that have used either surveys or laboratory sleep assessments to address this question have reported that sleep time is reduced in the elderly; however, other studies have reported no change or even an increase in sleep time. Consolidation of such findings is difficult because the results are complicated by whether total sleep time was assessed objectively or was self-reported and whether daytime napping was included, given that ~15% of people aged over 55 years are reported to nap four to seven times per week.<sup>22</sup> One current view is that total sleep time may not necessarily decrease with age, but the way in which sleep is consolidated becomes altered (i.e., daytime napping). Such a hypothesis is strengthened by findings that elderly individuals are sleepier during the day, measured by tests like the multiple sleep latency test, indicating a reorganization of sleep disruption. On the one hand, there is evidence that napping in healthy individuals improves daytime functioning.<sup>23</sup> On the other hand, there is evidence that napping is associated with a higher risk of all-cause mortality in some studies.<sup>24–26</sup> Although excessive daytime somnolence is common in the elderly and may be indicative of cognitive impairment,<sup>27</sup> it is often secondary to a comorbidity and its treatment or an underlying sleep disorder.<sup>28</sup> Thus, when sleep need is assessed by both total sleep time and daytime functioning, healthy elderly people are no sleepier than their younger counterparts. Interestingly, a recent study by Duffy et al<sup>29</sup> showed that healthy elderly individuals were less sleepy and performed better in tests of alertness and attention than young subjects after sleep deprivation supporting the concept that sleep need may reduce with age. Of note though, a recent Spanish study investigating sleep duration in the elderly

has shown that health-related quality of life was reduced at sleep durations less than or greater than 7 hours, particularly at the extreme sleep durations (<5 h and >10 h).<sup>30</sup>

## CHANGES IN SLEEP QUALITY AND CIRCADIAN RHYTHMS

Along with the reported changes in sleep architecture come reports of decreasing sleep quality. More specifically, difficulties in initiating sleep have been reported in 13 to 45%, disrupted sleep in 20 to 65%, early morning awakening in 15 to 54%, and nonrestorative sleep in 11%<sup>31</sup> of older adults. The question then remains: Are these changes in sleep quality simply a part of aging, or are they secondary to other comorbidities that arise with advancing age? Much of the evidence points to the latter. For example, after controlling for comorbidities (e.g., chronic pain, depression, heart disease), the high rates of insomnia reported in the elderly population become considerably lower. The age-related increase in insomnia is abolished when social satisfaction and activity status are considered using adequate statistical control.<sup>32</sup> This finding is further supported by a study of 11,924 Canadians, which showed no association between aging and insomnia.<sup>33</sup> Importantly, reductions in reported difficulties of sleep initiation and maintenance are associated with improved health.<sup>34</sup> Foley et al<sup>35</sup> reported that from a cohort of over 9000 people over 65 years of age, only 12% reported an absence of sleep complaints, but that aging generally was not associated with more frequent complaints after adjusting for health status. In addition, Vitiello et al<sup>36</sup> found in two large research cohorts that only 1.35% and 3.14% of adults >60 years of age had major sleep complaints or disorders after screening for medical and psychiatric illnesses. Lastly, data from the 2003 National Sleep Foundation Survey from people aged 55 to 84 years revealed that ~40% of those with major comorbidity perceived their sleep to be of only fair to poor quality.<sup>37</sup> This is striking when compared with those without medical conditions in whom only 10% perceive their sleep quality as fair to poor. Combined, these epidemiological studies suggest that many of the age-related sleep problems are secondary to medical illness rather than to aging per se. Although much of the increased prevalence of insomnia in the elderly is secondary in nature, primary insomnia can still occur. Treatment of primary insomnia was recently reviewed<sup>38</sup> and can involve both nonpharmacological and pharmacological therapy. Nonpharmacological therapy, such as cognitive behavioral therapy, is effective but can be time consuming and difficult to employ in the primary care setting. Pharmacological options include hypnotics, which have been shown to be beneficial in the treatment of insomnia in the elderly, although safety profiles require monitoring.

In addition to changes in sleep quality, elderly individuals often tend to go to bed earlier and wake up earlier when compared with younger individuals. Although this finding was originally attributed to a phase advance of the circadian oscillator,<sup>39,40</sup> recent evidence suggests that the age-related advance in sleep-wake timing may result from an inability to sustain sleep at particular circadian phases or be attributed to the presence of evening napping and advanced illumination.<sup>41,42</sup> Advanced age is characterized by a deterioration of the circadian variation of many physiological processes that play an important role in homeostasis (e.g., sleep-wake cycle, core body temperature, performance, alertness, and secretion of many hormones). In humans the circadian rhythm is generated by the circadian pacemaker that is situated in the suprachiasmatic nucleus (SCN) of the hypothalamus and synchronized to 24 hours, primarily by the light-dark cycle acting via the SCN. Aging is associated with malfunction or decrease in sensitivity of the SCN to environmental cues to adjust circadian rhythm to a natural 24-hour day/night cycle, which may explain why older people are generally less tolerant of shift work and jet lag. One key sleep-promoting hormone, melatonin, is released in the evening during darkness. Melatonin concentrations decrease from puberty, eventually reaching levels similar to daytime concentrations in old

age,<sup>43</sup> which may contribute to the increased frequency of sleep-related disorders with aging.<sup>44</sup>

### Other Factors Influencing Sleep Problems in the Elderly

Behavioral and environmental factors may also contribute to the frequent awakenings and the inability to sleep well in the elderly. Poor sleep hygiene, dietary habits, excessive daytime napping,<sup>22</sup> and increased nocturia<sup>45</sup> may be detrimental to nocturnal sleep. Environmental factors such as noise can affect the quality of sleep,<sup>46</sup> particularly because elderly individuals have more N1 and N2 sleep, and may be responsible for causing further arousals and disruption in the elderly. In addition, elderly individuals experience a higher prevalence of medical conditions that make sleep consolidation difficult, including chronic cardiac or pulmonary disease, and any condition associated with chronic discomfort, such as arthritis. Unfortunately, medications taken for the symptoms of these conditions may also promote insomnia. The prevalence of several sleep disorders also increases with aging, including restless legs syndrome and REM behavior disorder. Furthermore, a common sleep disorder that impairs an elderly individual's ability to achieve consolidated sleep is sleep-disordered breathing.

**SLEEP-DISORDERED BREATHING**—Sleep-disordered breathing (SDB) is a broad term that encompasses a range of breathing disorders, from primary snoring through to upper airways resistance syndrome and *obstructive* sleep apnea. Less common, but seen primarily in the aging person, is *central* sleep apnea, which is often associated with CHF.

**OBSTRUCTIVE SLEEP APNEA**—Obstructive sleep apnea (OSA) is a common syndrome in the middle-aged U.S. population, being present in at least 4% of adult men and 2% of adult women.<sup>47</sup> The disorder is characterized by repetitive collapse (apnea) or partial collapse (hypopnea) of the pharyngeal airway during sleep.<sup>48–51</sup> These airway obstructions lead to increasingly powerful respiratory efforts until the airway reopens and breathing is restored, often in association with an arousal from sleep (Fig. 2). These transient events also expose the sufferer to intermittent hypoxia and hypercapnia, large swings in intrathoracic pressure, as well as surges in sympathetic activation, all of which have important deleterious consequences.

### Effects of Aging on the Pathophysiology of OSA

Aging is known to be a major factor contributing to the risk of OSA, with increases in age associated with apnea prevalence. Ancoli-Israel et al found that 62% of community-dwelling individuals over 60 years of age had a respiratory disturbance index  $\geq 10$ /h (number of apneas and hypopneas per hour of sleep).<sup>52</sup> Similarly the Sleep Heart Health Study, one of the largest epidemiological studies to date, found stepwise increases in the prevalence of SDB with advancing age; it is noteworthy that  $\sim 20\%$  of subjects aged over 60 years had an RDI  $\geq 15$ /h.<sup>53</sup> In addition, Mehra et al recently showed that 26% of older men in a large cohort of almost 3000 had an RDI  $\geq 15$ /h, with aging being an independent risk factor in multivariate logistic regression analyses. Even individuals who are healthy, nonobese, and asymptomatic for OSA demonstrate a marked increase in the respiratory disturbance index with age, especially for men.<sup>54,55</sup>

The exact mechanisms whereby aging increases the risk of OSA are not completely understood. Although several physiological factors or phenotypical traits have been identified, the amount each trait contributes to an individual's OSA is likely to vary with different combinations of traits that are present in each patient. The majority of data suggest that an anatomically small pharyngeal airway is a key factor in the development of upper airway (UA) obstruction with pharyngeal dilator muscles compensating for the anatomical

deficiency during wakefulness, but not during sleep. The ability to maintain a patent airway is a balance between (1) the amount of soft tissue located in the bony compartment created by the mandible and spinal column and (2) the ability or strength of the pharyngeal dilator muscles to contract. It is therefore not surprising that many OSA patients have a reduced airway lumen due to increased soft tissue and a compromised pharyngeal anatomy. In addition to UA anatomy, several phenotypic traits are likely to be important: the ability of pharyngeal dilator muscles to respond to chemical and mechanical stimuli during sleep, the ease with which arousal from sleep is triggered by obstructed breathing efforts (arousal threshold), changes in lung volume and recoil (since increased end-expiratory lung volume can tether open the upper airway) and the effect of ventilatory control stability (loop gain). It is likely that aging may be associated with important changes in one or a combination of the factors that may contribute to OSA in such groups (summarized in Fig. 3).

**UPPER AIRWAY ANATOMY AND COLLAPSIBILITY**—The UA in the human is composed of numerous muscles and soft tissue but lacks bony or rigid support. As such there are several anatomical and physiological influences that bias toward a collapsible airway. Perhaps the most obvious factor predisposing to OSA is the size or caliber of the airway; a large airway will be less prone to collapse than a small airway. Most studies that have examined age-related changes in the UA have used imaging techniques such as magnetic resonance imaging (MRI) or computed topography (CT) and acoustic reflection. Malhotra et al used MRI studies of the upper airway and observed increased deposition of parapharyngeal fat in healthy older individuals as compared with younger controls<sup>56</sup> that was independent of body mass index (BMI), suggesting a preferential deposition of parapharyngeal fat with aging. Furthermore, Martin et al measured UA caliber using acoustic reflection in 114 subjects over the age range of 16 to 74 years and found that all UA dimensions, except at the oropharyngeal junction, decreased modestly with age.<sup>57</sup>

There has also been controversy in the published data regarding the effects of aging on pharyngeal resistance and collapsibility, with some groups showing similar findings in older versus younger individuals, whereas others have reported pharyngeal compromise in the elderly.<sup>57–60</sup> Eikermann et al<sup>61</sup> recently observed increased pharyngeal collapsibility during sleep in older as compared with younger individuals. However, an increase in the predisposition to pharyngeal collapse due to anatomy has not been shown in all investigations. Mayer et al measured airway size using CT and reported that older patients (>63 years) had larger UAs at all pharyngeal levels than the youngest group of patients (<52 years).<sup>62</sup> Similarly, Burger et al reported an increase in pharyngeal airway lumen area with aging at functional residual capacity (FRC); however, only normal subjects were included, potentially leading to influences of survivor effects and selection bias.<sup>63</sup> Thus it is difficult to draw firm conclusions from the available imaging data about the changes in upper airway and the predisposition toward collapse with age.

In addition to the size of the airway, the length of the airway has been suggested to also be an important predisposing factor to the pathogenesis of OSA, especially in males.<sup>64</sup> Specifically, it has been proposed that as the length of the airway increases, it becomes more prone to collapse. Such an effect is not simply limited to males because some data have shown that there are changes in pharyngeal airway length at menopause that likely adversely affect pharyngeal mechanics in females.<sup>56,64–66</sup> As such, the current data suggest that changes in the length of the airway may be important in the predisposition to OSA with aging.

**UPPER AIRWAY DILATOR MUSCLE ACTIVITY**—UA patency depends not only on the anatomy of the UA but also on the ability of the UA dilator muscles to be recruited. Unfortunately, there have been only a few studies addressing the impact of aging on

pharyngeal dilator muscle function and responsiveness. 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.<sup>56,67</sup> Although such studies recently reported marked impairment in UA protective reflexes in association with aging, these studies were conducted in healthy subjects during wakefulness. Whether aging influences on pharyngeal airway dilator muscle recruitability are important in mediating pharyngeal compromise in the elderly is also unclear. One report demonstrated a diminished genioglossus muscle response to hypoxia in association with aging, although the mechanistic importance to OSA of this observation is unclear.<sup>68</sup> Nonetheless, taken in aggregate, the current evidence strongly suggests that the anatomical susceptibility (i.e., UA anatomy and physiology) to OSA appears to worsen with age.

**LUNG VOLUME CHANGES**—The indirect effect that changes in lung volume have on airway patency is also an important factor. 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,<sup>69,70</sup> all of which may assist in patency. There have been several important human studies that have suggested that increases in end-expiratory lung volume can provide a protective influence on the UA.<sup>71,72</sup> Furthermore, studies have demonstrated that manipulations in end-expiratory lung volume during sleep have a marked effect on pharyngeal collapsibility in controls and those with OSA.<sup>73–75</sup> There are also data demonstrating that the FRC is reduced in supine obese patients<sup>76</sup> and that FRC tends to decrease following sleep onset.<sup>77</sup>

Lung compliance is known to increase with aging as a result of airspace dilatation and remodeling of lung parenchyma (“senile emphysema”).<sup>78,79</sup> Furthermore, obesity can cause reductions in the FRC, which may also increase the propensity for pharyngeal collapse. The existing data might therefore suggest that aging-related decrements in lung elastic recoil could compromise pharyngeal mechanics.<sup>80,81</sup> In theory, older individuals may have less lung volume tethering on the UA than younger individuals.<sup>78,79</sup> However, there have been no systematic studies addressing the hypothesis that the aging predisposition to pharyngeal collapse is mediated (at least in part) via reduced end-expiratory lung volume tethering during sleep reported to date.

**AROUSAL THRESHOLD**—Arousals from sleep due to UA obstruction occur when ventilatory drive reaches a certain threshold: often termed the arousal threshold.<sup>82</sup> The arousal from sleep is an important protective mechanism used to reopen the obstructed airway and ameliorate the hypoxemia associated with the hypopnea or apnea. However, the aging effects on arousal threshold have been minimally studied. Indeed, elderly people are known to have an increased number of spontaneous arousals from sleep,<sup>11,83,84</sup> suggesting that older adults may have a lower arousal threshold. In contrast, recent studies examining how the arousal threshold changes with age have found no difference,<sup>61,85</sup> suggesting that aging does not have a major impact on the threshold. Thus controversy remains regarding aging effects on arousal threshold.

**VENTILATORY CONTROL STABILITY OR LOOP GAIN**—The stability of the respiratory control system is also an important factor in the pathogenesis of OSA.<sup>86</sup> The stability of the ventilatory system is often described using the engineering concept of loop gain (LG). LG is formally defined as a unitless number that characterizes the sensitivity of control systems with negative feedback. In respiratory control, LG is the product of the combined sensitivity of the peripheral and central chemoreceptors (i.e., controller gain) and the efficiency of the lungs and muscles that produce ventilation to determine the level of O<sub>2</sub> and CO<sub>2</sub> in the blood for any given ventilatory drive (i.e., plant gain). Mathematically, LG

can be defined as the size of a ventilatory correction or response divided by the size of the disturbance prior. For example, if ventilation is disturbed in some way, such as by a hypopnea, there will be a fall in arterial O<sub>2</sub> and a rise in CO<sub>2</sub>, and ventilation will increase as a consequence when the event is terminated. If the magnitude of the response is larger than the disturbance then LG will exceed 1, and breathing disturbance will grow in amplitude and result in unstable breathing. Conversely, if LG is less than 1, breathing will remain stable.

There are several features of the ventilatory pattern in elderly individuals which suggest that the chemical control of breathing is unstable. For example, an increased proportion of central apneas in elderly patients with sleep apnea have been reported.<sup>52,87–89</sup> Furthermore, when compared with healthy young adults, the prevalence of periodic breathing in the elderly is increased, especially in those with CHF<sup>90</sup> (see later discussion). Importantly, if the stability of the respiratory controller decreases with age, it could contribute to the increased prevalence of OSA in the elderly. In contrast, studies have shown that chemosensitivity is actually unchanged<sup>91</sup> or even reduced with age.<sup>92–94</sup> Although chemosensitivity is only one factor that contributes to the chemical control of breathing, studies of chemosensitivity suggest that the system actually becomes more stable with age. In accordance with such studies, a recent investigation demonstrated that LG values for healthy, elderly patients with or without OSA (when measured with the proportional assist ventilation technique) were quite low.<sup>95</sup> Although this study was limited by the small number of elderly patients with OSA that were studied, the data indicate that ventilatory control is quite stable in the elderly. This finding, combined with the uncertainty surrounding the role of changes in the arousal threshold with advancing age, suggests that OSA in the elderly can primarily be attributed to changes in the anatomy and physiology of the UA.

### Consequences of OSA

The consequences of OSA fall broadly into two domains: (1) neurocognitive dysfunction, such as excessive daytime sleepiness and decreased quality of life resulting from sleep fragmentation<sup>96–98</sup> and (2) metabolic dysfunction<sup>99–101</sup> and cardiovascular disease (including atherosclerosis, stroke, myocardial infarction, hypertension, and CHF), which are likely the result of the intermittent hypoxia and sympathetic stimulation during OSA.<sup>48,102,103</sup> Although the prevalence of OSA tends to increase with age, a recent report demonstrates that the clinical significance and severity of OSA may actually decrease.<sup>104</sup> Interestingly, although OSA probably results in increased morbidity and mortality during middle age, it has been suggested that OSA may have a protective role in patients aged 70 years,<sup>105</sup> perhaps due to underlying factors that enhance survival or as a result of the development of protective mechanisms. However, such a proposal still remains controversial because the effects that aging has on such consequences of OSA are complex and not necessarily independent of each other.

**NEUROCOGNITIVE FUNCTION**—Cognitive impairment is known to increase with age, from a prevalence of up to 19% in individuals <75 years to 29% in those >85 years.<sup>106</sup> Furthermore, 47.2% of individuals over the age of 85 years are known to have dementia, including Alzheimer disease.<sup>107,108</sup> Because SDB is more prevalent in the elderly, it is plausible that the presence of a sleep disorder could worsen dementia. SDB occurs more frequently in patients with Alzheimer disease than in nondemented older subjects, and its severity is correlated with the degree of cognitive impairment in this group. Interestingly there is limited evidence that treatment of sleep apnea may reverse some symptoms of dementia in some studies.<sup>109</sup> and it has been suggested that practitioners should consider SDB in the differential diagnosis of reversible dementia in older patients.<sup>110</sup>



In middle-aged individuals, good evidence shows that the intermittent hypoxemia and arousals associated with frequent airway obstructions result in fragmented sleep and contribute to impaired cognitive functions such as memory, attention, and learning.<sup>96–98</sup> However, the association between OSA and neurocognitive impairment in elderly individuals is complex, and may be confounded by the increased prevalence of other comorbidities.<sup>109,111,112</sup> Two studies in a group of elderly Japanese American men have reported no association between SDB and cognition,<sup>34,113</sup> whereas several other studies have reported that the presence of SDB in the elderly increases the risk of cognitive impairment,<sup>27,112,114</sup> especially in older women.<sup>115</sup> Additionally, some studies have suggested common genetic features that link OSA and dementia based on ApoE genes.<sup>115,116</sup> Another possibility is that some dementia patients actually have pseudodementia that is caused by depression, a condition whose incidence is known to increase in incidence with untreated sleep apnea.<sup>53</sup> As such, the mechanism underlying the link between these two disorders still requires further investigation.

**OBESITY AND METABOLIC DYSFUNCTION**—Obesity is one of the most common public health issues that the developed world faces and is well known to be linked to the prevalence of OSA.<sup>117</sup> Aging may increase the risk for OSA because the prevalence of obesity increases in the elderly.<sup>117</sup> Indeed, a recent study followed 427 community-dwelling elderly individuals for 18 years to examine the natural history of SDB. The authors reported that the observed changes in RDI were associated with changes in BMI, independent of age.<sup>118</sup> Undoubtedly the presence of obesity imposes a mechanical disadvantage to the upper airway (i.e., increased fat around both the UA and the trunk promotes UA collapse and reduced FRC). Obesity also strongly increases the risk for the development of metabolic syndromes such as insulin resistance and glucose intolerance, both of which are more prevalent in the elderly.<sup>119,120</sup> A recent investigation showed a similar age-related increase in the number of individuals with metabolic syndrome as compared with those with OSA.<sup>121</sup> Furthermore, the presence of OSA, independent of obesity, is also a very strong risk factor for the development of adult-onset diabetes as well as a variety of adverse cardiovascular outcomes such as hypertension.<sup>122,123</sup> Because the potential for serious OSA-related cardiovascular events may increase with advanced age, these findings have important implications for the elderly.<sup>124</sup>

### **SYSTEMIC HYPERTENSION AND OTHER CARDIOVASCULAR**

**CONSEQUENCES**—Although there are many studies highlighting the association between cardiovascular morbidity in the middle-aged population,<sup>125–128</sup> very few studies have specifically investigated the cardiovascular sequelae in the aged. While there is strong evidence for a link between OSA and hypertension in the middle-aged, interestingly this may not hold true for the elderly. Haas and colleagues<sup>129</sup> conducted a large cross-sectional analysis of 6120 participants of the Sleep Heart Health Study and found no significant relationship between hypertension and SDB in those who were over 60 years of age. Because this study was not longitudinal, it is possible that this finding may have been confounded by a survivor effect; that is, the elderly subjects sampled might have been inherently less susceptible to the adverse effects of OSA versus young to middle-aged people. However, a recent study suggested that the lack of association between hypertension and OSA in the elderly may be due to the reduced heart rate and blood pressure responses associated with arousal.<sup>130</sup> These relatively new findings demonstrate the need for new studies that investigate the effect of treatment of OSA on cardiovascular outcomes in the elderly.

There is also good evidence in the literature which demonstrates that OSA may worsen left ventricular function and contribute to the development of CHF.<sup>131,132</sup> Cross-sectional data from the Sleep Heart Health Study demonstrated that individuals are 2.38 times more likely

to have heart failure in the presence of OSA defined as an AHI >11/h, which was the largest cardiovascular risk reported.<sup>131</sup> A recent, prospective longitudinal study in a population-based cohort of subjects ranging from 70 to 100 years of age demonstrated that the presence of severe OSA increases the risk of ischemic stroke in the elderly.<sup>133</sup> In elderly individuals, the presence of heart failure is linked to myocardial infarction and atrial fibrillation,<sup>134</sup> which are also linked to the presence of OSA.

## CONGESTIVE HEART FAILURE AND CENTRAL SLEEP APNEA

CHF is a condition that affects more than 5 million individuals in the United States. Despite available treatments, CHF is still associated with major morbidity and mortality. Significant reduction in cardiac output causes an accumulation of blood in the veins and can lead to lung congestion, which may progress to pulmonary edema. Edema may be localized to the extremities in right heart failure, but it may also cause pulmonary congestion and interfere with the regulation of breathing in addition to causing orthopnea. Patients with CHF may have a variety of sleep-related problems, such as disrupted sleep, reduced sleep efficiency, paroxysmal nocturnal dyspnea, and a general feeling of fatigue.<sup>135</sup> Furthermore, the appearance of OSA and central sleep apnea (CSA) is quite common in patients with CHF,<sup>135–138</sup> although the relative prevalence of CSA versus OSA varies across studies.<sup>90,139–141</sup> Because considerable overlap exists in the pathogenesis of OSA and CSA, CHF may be associated with both conditions, although for this section we will focus primarily on CSA. CSA in patients with CHF often manifests as a type of periodic breathing called Cheyne–Stokes respiration (commonly referred to as CSA-CSR), which is characterized by a cyclic pattern of waxing and waning breaths with periods of apnea (Fig. 4). In contrast to OSA, CSA-CSR is specifically defined by a lack of respiratory effort during the phase of zero airflow, resulting in repetitive periods of insufficient ventilation and compromised gas exchange. Furthermore the cycle time of CSA-CSR is quite long (60 to 90 seconds) as compared with other forms of CSA.

### The Effects of Aging on the Pathophysiology and Consequences of CHF and CSA-CSR

CSA-CSR has long been established to be due to instability in feedback control involved in the chemical regulation of breathing.<sup>142–144</sup> It is well documented that all CHF patients have increased circulation delays, and those with CSA-CSR often have increased controller gains<sup>135,145</sup> (i.e., increased peripheral chemosensitivity), and both would be predicted to increase LG, thus contributing to the development of CSA-CSR. However, because the prolonged circulation delays are similar in CHF patients with and without CSA-CSR, circulation delay is thought to be a predisposing factor rather than causal. Additionally, decreases in lung volume associated with the supine position (a factor that increases the plant gain because it reduces the capacity to dampen oscillations in PaO<sub>2</sub> and PaCO<sub>2</sub>) may help explain the increased propensity for CSA in this position.<sup>146</sup> However, the contribution of plant gain to the genesis of CSA-CSR in CHF has been suggested to be less important when compared with increases in delay and chemosensitivity.<sup>144</sup> There are several other factors associated with CHF that may predispose such patients to CSA-CSR, such as hypocapnia and decreased cerebrovascular reactivity to CO<sub>2</sub>. Patients with CSA-CSR have significantly lower PaCO<sub>2</sub> both awake and asleep due to the chronic hyperventilation when compared with CHF patients without CSA-CSR.<sup>135,147</sup> Such hyperventilation may be caused by increased controller gain, increased adrenergic stimulation, or stimulation of vagal and irritant afferents by pulmonary congestion and edema. Nonetheless, such hypocapnia places patients close to their apneic threshold and increases the propensity for apnea.

Aging is known to be a major factor affecting the risk of CSA-CSR associated with CHF. This was best characterized by a comprehensive study that examined 450 patients with CHF, and showed that age >60 years was a major risk factor for CSA-CSR in CHF patients.<sup>90</sup>

Other factors that have been independently associated with the presence of CSA-CSR in patients with systolic heart failure are male sex, awake hypocapnia ( $\text{PaCO}_2 < 38$  mm Hg), and the presence of atrial fibrillation and ventricular arrhythmias.<sup>136,140,148</sup> A current topic that is still under debate is whether CSA-CSR is simply a consequence of poor cardiac function, or whether CSA-CSR exerts an independent effect on the failing heart. In accordance with the former, the normal aging process is characterized by cellular, functional, and structural changes that bias toward cardiomyopathy. For instance normal aging has been shown to result in decreases in diameter and wall thickness of the arteries, which causes stiffening of the arterial walls, decreased volume elasticity, and increased blood pressure. When normal aging is compounded by the addition of one or more types of organic heart disease, such as CHF, it can lead to further deterioration of function. An investigation of 128 CHF patients admitted to hospital reported that elderly patients with CHF had relatively greater vasoconstriction (or decreased compliance) and blunted heart rate responsiveness associated with increased circulating norepinephrine when compared with younger patients with CHF.<sup>149</sup> Another contributing factor to the progression of myocardial failure and premature mortality may be the presence of any undiagnosed OSA. The presence of untreated OSA and the increased prevalence of OSA in the elderly may contribute to the development of heart failure. Further deterioration may cause the appearance of CSA-CSR. Once the abnormal pattern of breathing becomes established, it may play an important role in CHF progression, and most evidence suggests that the presence of CSA-CSR is associated with a significant increase in the risk for cardiac transplantation or death.<sup>150–152</sup>

### Treatment of SDB

To date, there is a paucity of data examining the treatment efficacy of SDB in older individuals. Continuous positive airway pressure (CPAP) remains the treatment of choice for individuals with OSA, but it is not always tolerated well, especially in the elderly. A recent, retrospective review of 44 older individuals with OSA showed that their CPAP adherence significantly declined with increasing age.<sup>153</sup> In contrast, another recent study reported that elderly individuals with both OSA and Alzheimer disease were able to tolerate therapeutic CPAP treatment,<sup>154</sup> suggesting that CPAP treatment may have benefits in certain elderly subpopulations. Other common treatments of SDB include the use of oral appliances or surgery. However, the practicality and the efficacy of such interventions in the elderly have not been thoroughly assessed. Conservative management of OSA through such things as weight loss, limiting alcohol consumption, and avoidance of the supine position during sleep should be stressed and recommended. Although less well studied in the elderly, certain myorelaxant hypnotics (e.g., benzodiazepines) may worsen apnea and should probably be avoided.<sup>155</sup>

The use of CPAP as a treatment has been widely studied for individuals with CSA-CSR. While it has been shown to be effective at reducing CSA-CSR in patients with CHF, the largest, randomized, multicenter trial that has been conducted to date did not show improved survival with CPAP use.<sup>156</sup> Because CPAP does not seem to reduce CSA-CSR for a large number of patients with CHF, other forms of treatment have been investigated. These include forms of noninvasive ventilation (i.e., adaptive pressure support ventilation), oxygen therapy and drugs such as theophylline,<sup>157</sup>  $\beta$ -blockers,<sup>158</sup> and acetazolamide<sup>159</sup> (all which may have efficacy in reducing CSA-CSR). Importantly, whether these treatments are as efficacious in elderly individuals remains an unresolved and important area of research. The current treatment of choice for CSA-CSR remains optimization of medical therapy for CHF.

## SUMMARY AND FUTURE DIRECTIONS

Aging is associated with a variety of changes that affect sleep and the emergence of sleep-disordered breathing. However, it is important to distinguish between treatable complaints and the normal age-associated changes in sleep patterns. Frequent arousals are common and should not necessarily prompt treatment interventions other than providing explanation and reassurance. Elderly patients should be advised that it is normal to awaken several times during the night, and that such awakenings will not seriously interfere with their next-day functioning as long as they can get back to sleep in a reasonable period of time. Quality and amount of sleep in the elderly is affected by many factors that include current medical conditions such as arthritis and depression as well as the presence of sleep-disordered breathing. The prevalence of SDB increases with advanced age regardless of the mechanism, although at a certain age it may become less harmful for the elderly. Future research is needed to improve the characterization of apnea phenotypes in the elderly as well as to determine whether the CSA-CSR is a consequence of CHF or contributes independently to the morbidity of CHF. Given the severe consequences associated with OSA and CHF, such research should focus on how to effectively treat such conditions. Lastly, because benefits of treatment may be modest in the elderly, treatment decisions need to be individualized for each patient.

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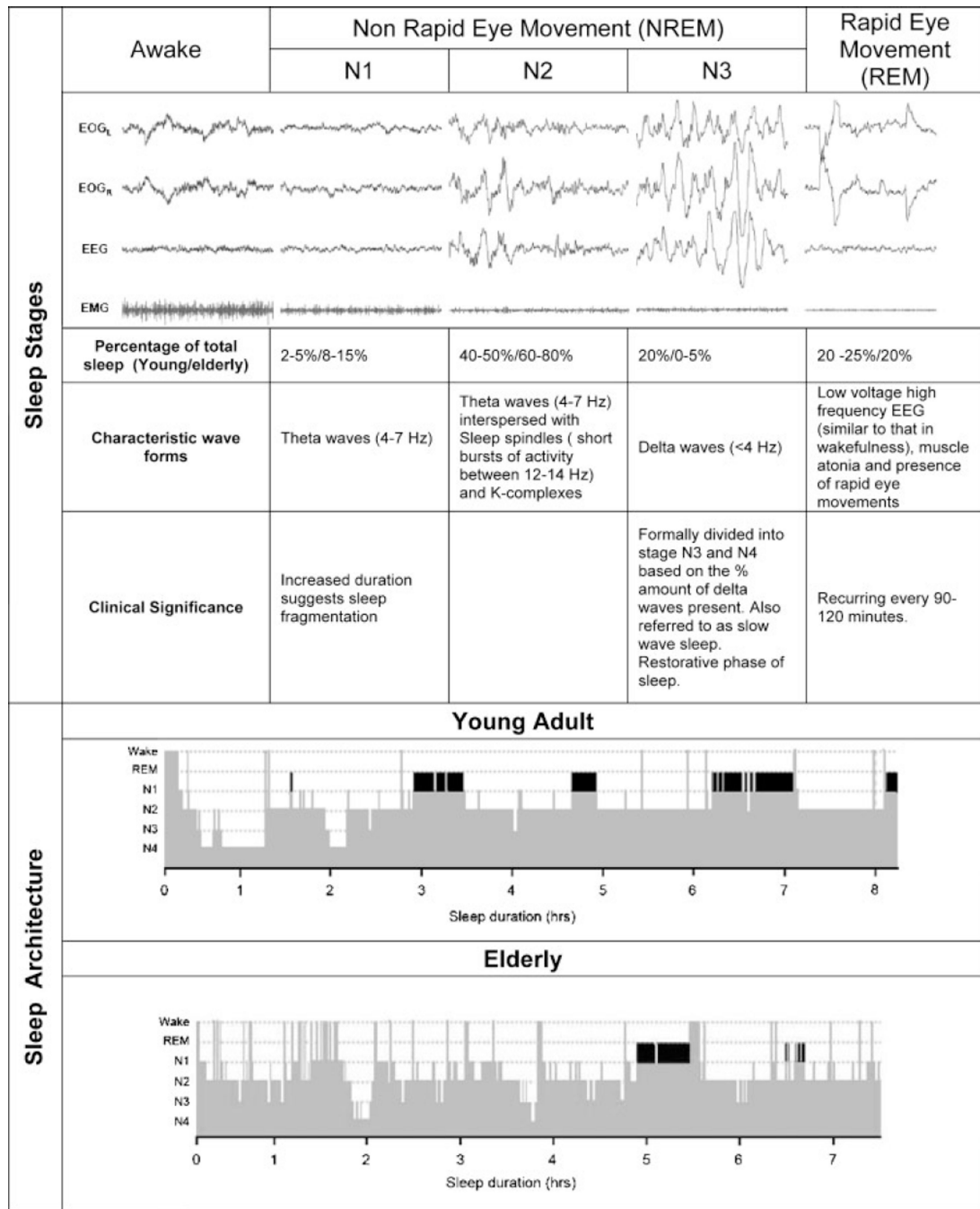
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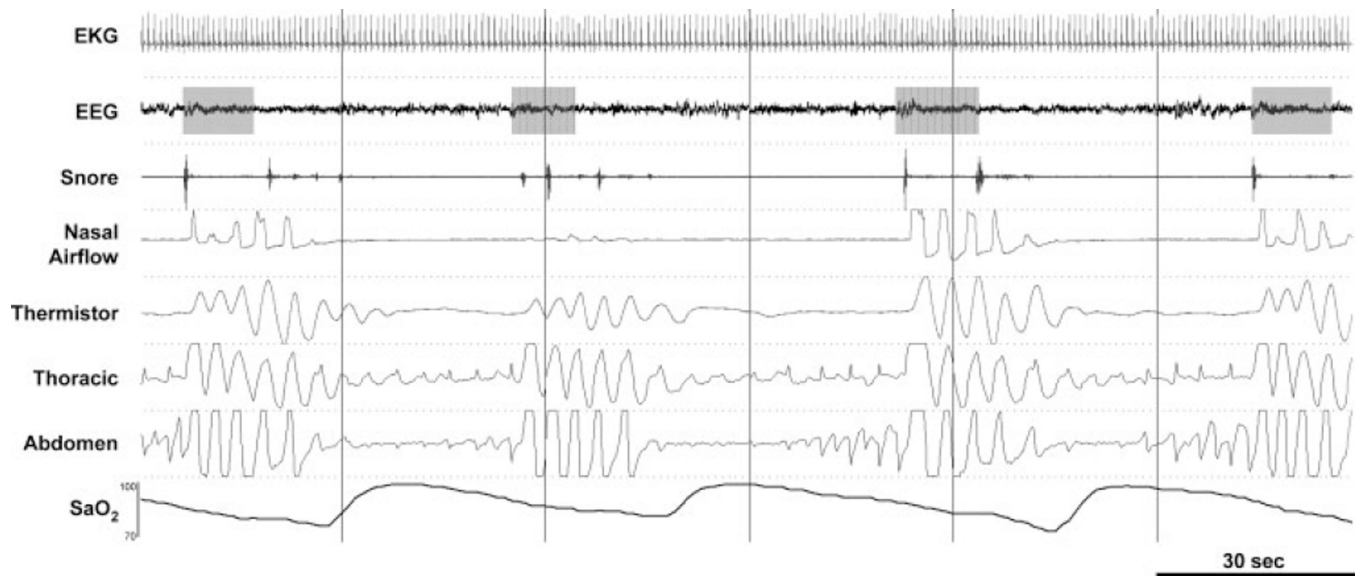
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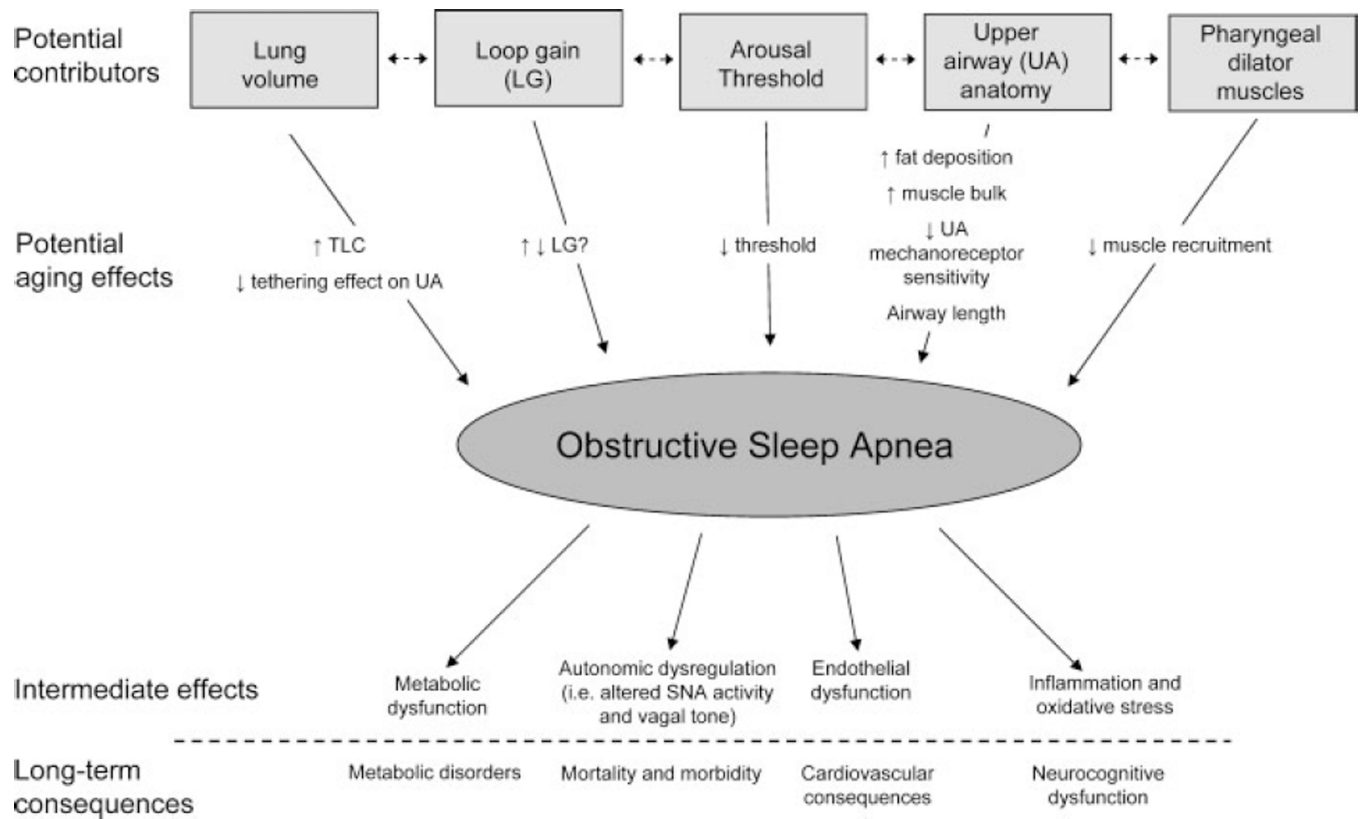


**Figure 1.** Effect of aging on the architecture of sleep. The top panel depicts the different stages of sleep and their associated characteristics. The bottom panel is an example of a typical hypnogram from a healthy young adult aged 24 years and a healthy elderly individual aged 72 years. It demonstrates the cycling between non-rapid eye movement (NREM) and rapid eye movement (REM) (black bars) throughout the night, with more stage 3 and 4 NREM sleep or slow wave sleep (SWS) during the early part of the night and the increased proportion of REM in the early hours. Note that elderly individuals have a reduction in SWS and REM as well as the frequent arousals/awakenings. N1–N4, non-rapid eye movement sleep stages 1 through 4.

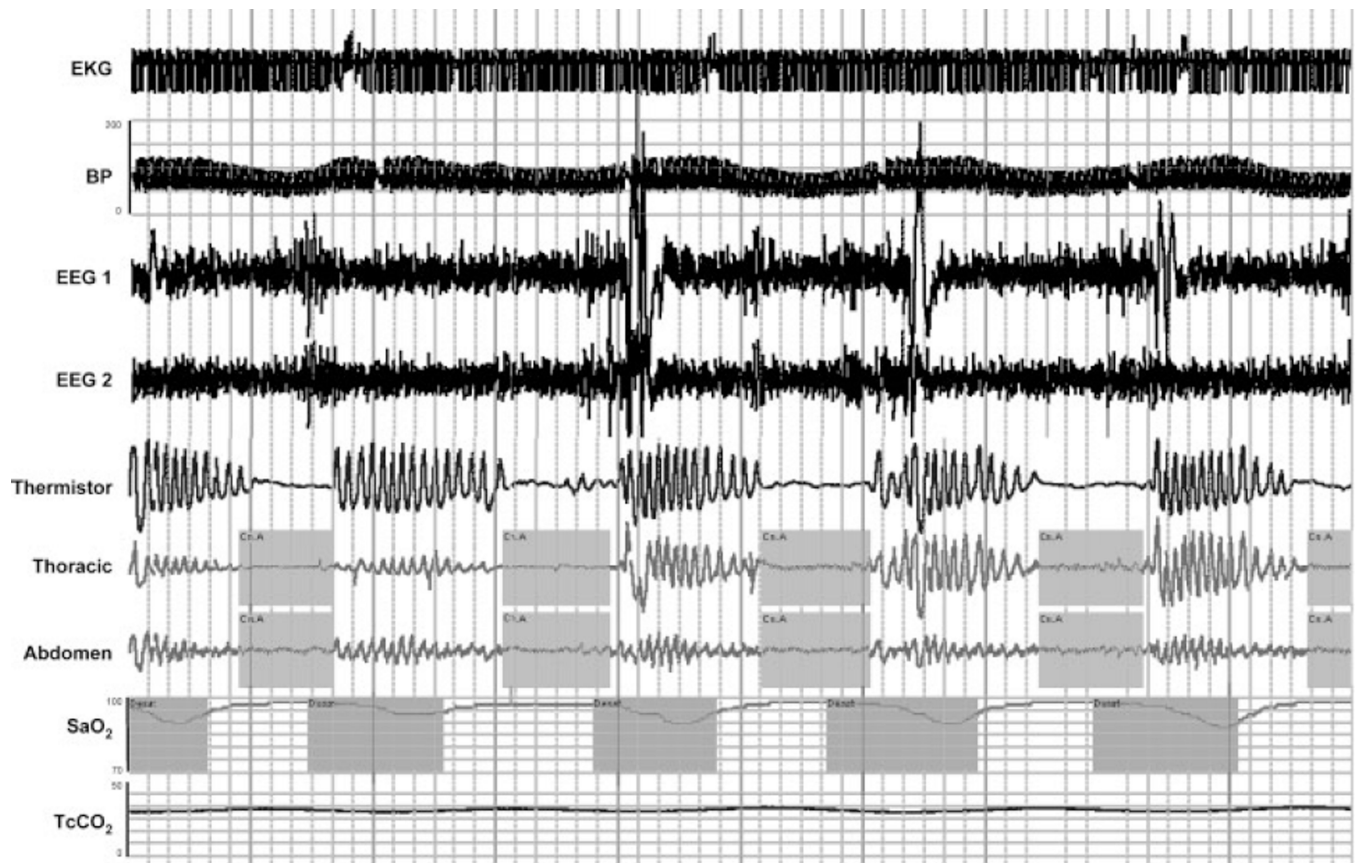


**Figure 2.**

An example of obstructive sleep apnea (OSA). Polysomnographic example from a clinical study in a patient with severe OSA (apnea/hypopnea index = 55.5 events per hour). Note that despite the repeated respiratory efforts to breathe (thoracic and abdomen), there is no nasal airflow, indicating the airway has become obstructed. Such obstructions are often associated with repeated oxygen desaturations and arousals (gray boxes) from sleep. EKG, electrocardiogram; EEG, electroencephalogram (C3-A2); SaO<sub>2</sub>, arterial blood oxygen saturation.



**Figure 3.** Summary of the potential aging effects on the pathogenesis of obstructive sleep apnea (OSA). Schematic of the various phenotypical traits or factors that contribute to OSA and how aging may affect them to increase the incidence of OSA in the elderly. Furthermore both the intermediate effects of OSA and the long-term consequences are also depicted. Refer to the text for further detail.



**Figure 4.**

An example of Cheyne-Stokes respiration associated with congestive heart failure. Polysomnographic example from a clinical study in a patient with congestive heart failure and central sleep apnea (CHF-CSA). Note the waxing and waning that occur in respiration and presence of repeated central apneas. Like OSA, the repeated apneas are often associated with repeated oxygen desaturations, arousals, and fluctuations in blood pressure and heart rate. EKG, electrocardiogram; BP, blood pressure; EEG, electroencephalogram (C4-A1, O2-A1); SaO<sub>2</sub>, arterial blood oxygen saturation; TcCO<sub>2</sub>, transcutaneous carbon dioxide.

**Table 1**

## Typical Changes that Occur in Sleep Patterns with Age

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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

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