CHEST™

OFFICIAL PUBLICATION OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

ONLINE FIRST

This is an Online First, unedited version of this article. The final, edited version will appear in a numbered issue of *CHEST* and may contain substantive changes. We encourage readers to check back for the final article. Online First papers are indexed in PubMed and by search engines, but the information, including the final title and author list, may be updated on final publication.

http://journal.publications.chestnet.org/

Online First articles are not copyedited prior to posting.

Word count: 1612

Point: Is the AHI the best way to quantify the severity of sleep disordered breathing? – YES

David M. Rapoport, MD
Division of Pulmonary, Critical Care and Sleep Medicine
New York University School of Medicine
NY, NY

Email: david.rapoport@nyumc.org

Address:
      Sleep Disorders Center
      Bellevue Hospital
      462 First Ave. Room 7N2
      New York, NY 10016

Over the past 30 years, we have come to appreciate that during sleep there is a spectrum of obstructive breathing physiology ranging from mild snoring to severe obstructive sleep apnea syndrome[1]. By some estimates significant abnormalities of breathing during sleep may affect as much as 15-20% of the adult population[2] and 5-10% of children.[3] The obesity epidemic makes it likely that these numbers will only increase.[4]

While describing single periods of obstruction to normal breathing (an "event") seems simple, we are still struggling to understand the clinical significance of *repetitive* obstructions – ie the sleep apnea/hypopnea syndrome. At one extreme we now know that during sleep normal individuals experience a small number of partial (hypopnea) or even complete (apnea) respiratory obstructions that may have little or no implications for their health[5,6]. At the other extreme, some severely affected individuals have virtually continuous 20-60 second cycles of obstruction during sleep and resumptions of breathing that occur up to 100 times per hour. These latter individuals almost all suffer severe psychophysiological[7], neurologic[8], cardiovascular[9-11] and other consequences that justify calling this "disease[1]," and these consequences appear to be markedly improved if the number of cycles (the apnea hypopnea index or AHI) is reduced by effective treatment[12-13].

Until now, we have used the AHI to measure where an individual lies on both the spectrum of their respiratory findings and of the syndrome. AHI counts the number of complete and partial obstructions that occur per hour of sleep, but many definitions have been proposed and this may account for some of the variability in assessing its value. In some definitions, only events with an associated oxygen desaturation are counted[15]. Other definitions count all events that produce physiologic response: in addition to oxygen desaturation, arousal on EEG, surrogates of arousal, changes in sympathetic activity like pulse, etc are used to "validate" a detected respiratory event and allow it to contribute to the AHI[14]. However, all definitions of AHI to date share the concept of defining severity of the syndrome by the *occurrence rate* of individual events that are deemed non-artifactual and "significant" (ie the event itself has a detectable consequence). As only rate of events is captured, it is clear that AHI incorporates severity of the individual events only to the extent that event severity correlates with their frequency. There are other, potentially independent, axes of event severity (eg the depth and duration of desaturation, the extent and duration of arousal, the level of sympathetic activation, etc) that *could* impact severity of the overall clinical *syndrome,* but to date there is no consensus, and only limited research, into their utility. Thus, must publications accept the AHI as the best available tool so far.

Two questions need to be asked of how well the AHI quantitates severity. The first is whether the current approach of using the rate of obstructive events (the AHI) to define the presence of "disease" is justified. Separately, one can ask how well AHI measures disease severity in those so diagnosed.

To diagnose disease using a continuous metric implies a model whereby there is a bimodal distribution of the metric where "disease" can be more or less separated from "normal" by a threshold value. As pointed out above, data in large populations shows AHI is rarely zero, even in normal individuals. The association of sufficiently elevated AHI with negative outcomes confirms there is some intensity of sleep disordered breathing event rate *that is abnormal*. However, as technology has led us to refine what events are being counted, little attention has been paid to changing this threshold value. It seems intuitive that the threshold of disease should change as we refine what is counted, but the values of 5 and 15 events per hour have been stubbornly present as "cut-points" above which we say sleep apnea syndrome is present. This has led to many of the objections to the value of the AHI (for diagnosis). If the "AHI" is made up only of complete or "severe" (eg. desaturating)

individual obstructions, perhaps a low value can provide a sufficiently specific indicator of disease. In contrast, if all subtle events that produce at least a minimal physiological consequences in the EEG or sympathetic nervous system are included, a somewhat higher value may increase sensitivity without too much loss of specificity. However, testing and refining these thresholds in clinical samples has been complicated by the extreme non-specificity of the outcome measures used to define the "gold standard" of "significant sleep apnea." Defining an epidemiologically "healthy" populations is critical to deciding on a threshold value for disease, and this varies with the outcome being evaluated (eg sleepiness or hypertension). Several studies have suggested that the "threshold" AHI number of events for "disease" is *not* low. For example the Sleep Heart Health Study showed a median AHI, by an inclusive definition, of nearly 30/hr in a large non-clinic population[16], and the Sao Paulo cohort recently reported that even in those with an AHI<5/hr and no daytime symptoms, evidence of upper airway collapsibility during sleep (flow limitation) was very prominent (the 95%ile cut off of flow limitation was 30% of the time asleep).[17] To reconcile these observations, I would argue that the AHI IS useful at its extreme values but less so in the mid-range. Despite evidence of widespread occurrence of obstructive events in the sleep of otherwise normal subjects, there is little doubt that if one compares those with a very low AHI (by any definition) to those with an elevated number (generally over 30/hr), excessive sleepiness, hypertension and other cardiovascular consequences are more frequent in the latter. Furthermore, many studies show improvement in clinical symptoms if the AHI is reduced by treatment in symptomatic subjects, again attesting to the ability of an elevated AHI to define disease[17]. However, rather than trying to find an exact cut-off between "normal" and "diseased," many of the same studies can be reinterpreted as showing that an intermediate AHI (ie between 5 and 30/hr, with some consideration of *which* AHI) confers no diagnosis, but rather a rising probability of disease defined by clinical outcomes. This reasoning is different from, but may underlie the common practice of diagnosing sleep apnea based on AHI alone if >15/hr, but requiring symptomatic consequences if between 5-15.hr. The situation is similar to the use of an elevated blood pressure taken in the clinic to define "hypertension." The cut off for hypertension was initially defined using measurements of blood pressure norms in large defined non-clinic populations. These values were validated when it was shown that "hypertension," ie an elevated measurement of blood pressure, had consequences for health. We now use intermediate blood pressures in a different way in those with other risk factors (eg diabetes, age) than in those who appear healthy. In a similar way, a high AHI is clearly a marker of disease. Thus I conclude AHI is a useful metric in defining the *presence* of obstructive sleep apnea if severely elevated, and useful to define the *risk* of obstructive sleep apnea if moderately increased.

This approach does not address the second question posed above: whether AHI measures severity of the disease once diagnosed. As the AHI increases, the *probability* of most sequellae increases, but there is a poor relationship of the frequency of respiratory events to the severity of the symptoms or findings. Multiple studies have shown that the correlation between AHI and sleepiness (either subjective or objectively measured by various tests) is poor if one looks only at those with diagnosed obstructive sleep apnea.[18] This is also true when the relationship of AHI to hypertension is examined: there seems to be a plateau of increased risk of hypertension above a threshold AHI of 5-15[19], with little further increase at higher AHI. There are also few data so far to suggest that *severity* of hypertension tracks the AHI. These observations are all compatible with the increasingly popular concept of differential susceptibility, ie that, rather than just being dependent on the "severity" implied by physiological challenge represented by the AHI, the genetic and environmental circumstances in an individual determine how much sleepiness, cardiovascular or other consequence will occur for a given challenge.[20]

In summary, the AHI is a useful metric in that it *defines* obstructive sleep apnea; it is limited in that it does not measure severity *well*. Unfortunately, to date it remains the *best*, and certainly the most used, metric for

severity. Perhaps this is because ipso facto, low AHI defines "normal," and high AHI "severely affected," leaving the "possibly susceptible" in a separate group. As a metric AHI is the polar opposite of tools like respiratory flow rate (FEV_1) as used in evaluating chronic obstructive lung disease (COPD): FEV1 does <u>not</u> *define* the presence of COPD (many other diseases – eg kyphoscoliosis and interstitial fibrosis - reduce flow rates by reducing lung volume). However, if limited to patients with COPD, FEV_1 is quite good at measuring severity of symptoms and of outcomes of the syndrome and operative mortality.

Until we finally understand the causes and mechanisms of differential susceptibility to sleep-related repetitive airway obstructions and arousals, the AHI continues to be the best we can do to evaluate patients with obstructive sleep apnea for diagnosis. We can use it to assess their susceptibility to long term consequences and to judge their response to therapy. However it remains poor for assessing the continuum of severity if by this we mean the severity of the other sequellae that are part of the syndrome. Finally, AHI remains an indispensable tool to probing the science of differential susceptibility: so far, at least, AHI is the best way to describe the physical "stimulus" that must be related to the "response" in the susceptibility equation.

References

1. 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. S*leep* 1999; 22:667-89.
2. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW Hla KM. Increased incidence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013; 177(9):1006-14.
3. Goodwin JL, Vasquez MM, Silva GE, Quan SF. Incidence and remission of sleep disordered breathing and related symptoms in 6-17 year old children – the Tuscon children's assessment of sleep apnea study (TuCASA). *J Pediatr* 2010; 157(1):57-61.
4. Young T, Peppard PE, Gottlieeb DJ. Epidemiology of obstructive sleep apena: a population health perspective. *Am J Respir Crit Care Med* 2002; 165(9):1217-39.
5. Redline S, Sanders M. Hypopnea, a floating metric: implications for prevalence, morbidity estimates, and case finding. *Sleep* 1997;20:1209-17.
6. Stradling JR, Barbour C, Glennon J, et al. Prevalence of sleepiness and its relation to autonomic evidence of arousals and increased inspiratory effort in a community based population of men and women. *J sleep Res.* 2000; 9:381-88
7. Ward KL, Hillman DR, James A, et al. Excessive Daytime Sleepiness Increases the Risk of Motor Vehicle Crash in Obstructive Sleep Apnea. Journal of clinical sleep medicine. *J Clin Sleep Med 2013*; 9:1013-21.
8. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med* 2010;182:269-77.
9. 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.
10. Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA*. 2012;307:2197-2198.
11. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010;122:352-60.
12. Gordon P, Sanders MH Sleep 7: Positive airway pressure therapy for obstructive sleep apnoea/hypopnoea syndrome. *Thorax* 2005; 60:68-75.
13. Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: results of a meta-analysis. *Arch Intern Med* 2003;163:565-71.
14. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur, VK et al. Rules for Scoring Respiratory Events in Sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events *J Clin Sleep Med*. Oct 15, 2012; 8(5): 597–619.
15. Iber C, Ancoli-Israel S, Chesson AL, Jr., Quan SF. for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
16. 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.
17. Palombini LO, Tufik S, Rapoport DM, et al. Inspiratory flow limitation in a normal population of adults in Sao Paulo, Brazil. *Sleep* 2013;36:1663-8.
18. Young LR, Taxin ZH, Norman RG, Walsleben JA, Rapoport DM, Ayappa I.Response to CPAP withdrawal in patients with mild versus severe obstructive sleep apnea/hypopnea syndrome. *Sleep*. 2013 36(3):405-12.
19. Nieto J, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea and hypertension in a large community-based study. *JAMA* 2000; 284(11):1829-36.
20. Van Dongen HP, Vitellaro KM, Dinges DF. Individual differences in adult human sleep and wakefulness: Leitmotif for a research agenda. *Sleep*. 2005; 28(4):479-96.

ONLINE FIRST

This is an Online First, unedited version of this article. The final, edited version will appear in a numbered issue of *CHEST* and may contain substantive changes. We encourage readers to check back for the final article. Online First papers are indexed in PubMed and by search engines, but the information, including the final title and author list, may be updated on final publication.

http://journal.publications.chestnet.org/

Counterpoint: Is the AHI the best way to
quantify the severity of sleep disordered breathing? No

Naresh M. Punjabi[1,2], MD

Departments of Medicine[1] and Epidemiology[2]
Johns Hopkins University
Baltimore, MD

Word Count: 1,786

Short Title: Limitations of the apnea-hypopnea index

Corresponding Author:
Naresh M. Punjabi, MD, PhD
Professor of Medicine and Epidemiology
Division of Pulmonary and Critical Care Medicine
Johns Hopkins Asthma and Allergy Center
5501 Hopkins Bayview Circle
Baltimore, Maryland 21224

Since the early clinical descriptions of obstructive sleep apnea in the 1970s, our understanding of the pathogenesis and adverse consequences of this chronic disease has advanced substantially.[1] Initially, the primary focus was the recognition of sleep-related apneic events which were observed to severely fragment sleep, induce cardiovascular instability, and lead to excessive sleepiness during the day.[2;3] Given the significant hemodynamic and sleep-related effects of obstructive apneas during sleep, it comes as no surprise that the "apnea index", which tallies the number of apneas per hour of sleep, became the primary disease defining metric for obstructive sleep apnea. However, over time as the full spectrum of upper airway collapse during sleep became more apparent, the simple concept of only quantifying apneas quickly evolved into something more complex.[4] It is now obvious that obstructive apneas, the original *sine qua non* for the disease, are not the only events of interest as obstructive hypopneas have similar effects (e.g., arousals, blood pressure swings).[4;5] As the clinical impact of hypopneas became widely recognized, these events were incorporated in quantifying disease activity and the original "apnea-index" gave way to the now commonly used "apnea-hypopneas index" (AHI). Although defining hypopneas continues to be plagued with many challenges,[6-8] the AHI has become a ubiquitous measure in sleep and respiratory medicine. In fact, the AHI is used not only to diagnose obstructive sleep apnea but also is central in assessing disease severity.

Since the initial formulation of the AHI, a large body of clinical and epidemiological has accumulated linking obstructive sleep apnea severity to numerous clinical outcomes including daytime sleepiness, impaired quality of life, motor vehicle accidents, incident hypertension, myocardial infarction, stroke, heart failure, diabetes, and all-cause mortality.[9-12] In most, if not all, of the available studies on the health significance of obstructive sleep apnea to date, the AHI has been used as the primary "exposure" or independent variable and correlated with specific outcomes of interest. Moreover, interventional studies, which have examined of the effects of positive airway pressure therapy, have also shown that treatment of varying degrees of sleep apnea, as indexed by the AHI, is associated with favorable effects.[13] Because of the consistency across studies in correlating the AHI with clinical sequelae, a strong foundation has formed supporting its use in characterizing obstructive sleep apnea. Indeed, advocates of the AHI often

1

cite the considerable evidence base of clinical outcomes to suggest that the AHI has criterion validity which is generalizable to several outcomes. While the argument that AHI is a valid measure of disease activity because it predicts the presence or development of clinical outcomes is reasonable, it is not without limitations and should be, at best, considered a crude and imprecise metric of obstructive sleep apnea.

Several lines of reasoning exist to refute the use of the polyomnogram-derived AHI as the "holy grail" for assessing obstructive sleep apnea. The first, and perhaps simplest, argument is that calculation of the AHI assumes that apneas and hypopneas are fundamentally equal in their biological effects. While evidence to date is limited on the relative contribution of apneas versus hypopneas in mediating clinical outcomes,[14] it is easily argued that because apneas occur as a consequence of the complete upper airway collapse, they may impose a greater pathophysiological impact (i.e., larger surges in sympathetic activity) than hypopneas that result from partial collapse of the upper airway. The lack of evidence examining the relative clinical impact of apneas and hypopneas does not necessarily obviate the concern that apneas and hypopneas are not pathophysiological equal. Second, it is now generally accepted that the clinical impact of obstructive sleep apnea is attributed, in part, to the cyclical hypoxemia associated with apneas and hypopneas. While the "H" part of the AHI certainly incorporates a component of oxygen desaturation, the threshold for the desaturation is quite arbitrary and there is little evidence to support a specific cut-point (i.e., 3%, 4%).[14;15] The choice of a desaturation threshold notwithstanding, an inherent problem with any threshold chosen is that it assumes that all hypopnea events that exceed the chosen threshold are equivalent. That is, a hypopnea with a 4% desaturation is considered biologically equivalent to a hypopnea that has a 8% or 10% oxygen desaturation. Certainly, greater degrees of hypoxemia are likely to have greater effects and as such the AHI disregards a crucial biological mechanism through which obstructive sleep apnea may arbitrate its adverse outcomes effects. Third, computation of the AHI also neglects the temporal distribution of the events. Apneas and hypopneas can occur evenly across the night or they can cluster during a particular segment of the sleep period. Events that temporally cluster may not have as large of an influence as events that are distributed throughout the night. For example, consider

2

two patients that have a total of 160 disordered breathing events over 8 hours of sleep. Although the AHI is exactly the same (~ 20 events/hr), events in the first patient are clustered within the initial two hours of sleep whereas in the second patient they are spread equally throughout the night such that the instantaneous rate at any time is 20 events/hr. It could be easily argued that the second patient may be more prone to the clinical effects of obstructive sleep apnea because the events disrupt the entire sleep period. In contrast, the first patient may not be as prone to the aforementioned health-related effects of obstructive sleep apnea because the concentrated "exposure" to disordered breathing events, although disruptive for the two hours of sleep period, still leaves the patient with a sufficient period of unperturbed sleep. While variants of AHI such as sleep stage-dependent AHI (NREM- and REM-AHI) and position dependent AHI (supine vs. non-supine) are used to capture the heterogeneity of sleep physiology, they do not entirely remedy the problem of temporal distribution of events. A fourth and relevant consideration in assessing the utility of the AHI relates to controversy that surrounds the definition of a hypopnea. Substantial disagreements remain regarding the degree of hypoventilation (or decrease in flow), severity of desaturation, and incorporation of arousals in defining a hypopnea. [6-8] Thus, can we really consider the AHI the ultimate criterion for characterizing obstructive sleep apnea if even the experts that utilize it cannot agree on an acceptable definition for a hypopnea? The lack of consensus is highly visible in the numerous hypopnea definitions that have been proposed and the rate at which these definitions have been changed just within the last few years. The fifth concern with the AHI as a metric for obstructive sleep apnea is that it is fraught with "errors of omission". The AHI, which tabulates the number of apneas and hypopnea, does not incorporate any information about the duration of apneas and hypopneas. It is inconceivable that an event lasting 10 seconds is physiologically equivalent to an event lasting 2 or 3 minutes. Figure 1 is a 10 minute sleep recording in a patient with obstructive sleep apnea. The AHI in this patient would be ~18 events/hr which certainly does not fully reflect that in this patient the events are long and associated with significant hypoxemia. Thus, omission of event duration information drills yet another hole in the armor of AHI as a disease-defining metric of absolute value. Another error of omission in the AHI is that it does not incorporate the increased work of breathing during sleep associated

3

with the occurrence of disordered breathing events. Complete or partial collapse of the upper airway increases the work of breathing which, in turn, results in acute cardiovascular effects (i.e., increased afterload) that may of clinical significance. Operationalizing any measure of disease presence or severity for obstructive sleep apnea should capture the pathophysiologic diversity of the disease process. The AHI falls far from this goal and is disappointing as a disease metric as it only provides a rate at which events occur during sleep.

Much of the foregoing discussion assumes that calculating a "rate" (apneas and hypopneas per hour of sleep), is an appropriate approach to characterize the severity of obstructive sleep apnea. Shahar[16] has recently argued that the use of the AHI as an exposure variable is rarely justified because it does not measure what it purports to represent. An argument is made that the frequency of disordered breathing events should be used as the exposure and not the rate at which these events occur (i.e., AHI). By calculating the AHI, bias is introduced which can be avoided by the use of alternative variables. Shahar[16] provides an illustrative example in which two patients have the same AHI but one sleeps 7 hours each night and the other sleeps 5 hours. Given that the AHI is similar in these two patients, the conclusion is that the exposure level based on the AHI is comparable which, in fact, is not true given that the cumulative number of events experienced by these patients is different because of differences in their habitual sleep time.
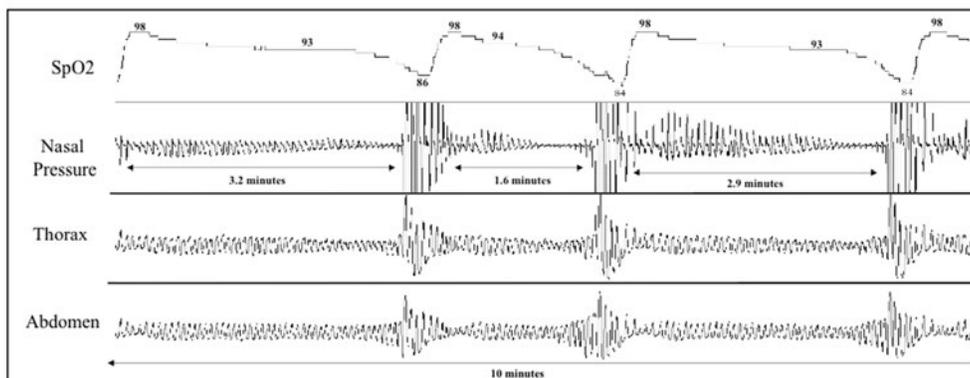
After decades of research, it is now accepted that obstructive sleep apnea is associated with major cardiovascular and non-cardiovascular endpoints. Given the wealth of accumulated evidence in the five decades after the initial clinical description of obstructive sleep apnea, we should have a robust disease defining measure. Unfortunately, that is not the case. While the AHI has generally served the sleep and respiratory community well, it is not without several major limitations. It is surprising that despite the amount of data collected during an overnight sleep study, the field has settled on one number (a rate) to characterize disease severity. Without doubt, using the AHI is a gross oversimplification of a complex disease phenomenon. When other disease states are examined, such oversimplification is not the case. Take the example of hypertension. Blood pressure is usually clinically represented by not one but several

4

metrics (e.g., systolic, diastolic, average). The field of sleep disorders medicine should not settle for taking a large series of time varying signals from the polysomnogram that often exceed one gigabyte of data and just use one metric to summarize all key features. Certainly, a "one size fits all" solution will never exist that can embody the physiologic diversity of apneas and hypopneas. It is time for sleep and respiratory medicine to accept the fact that the AHI is a parameter that crudely integrates the pathophysiology of obstructive sleep apnea. It is likely that several different parameters are needed to reflect disease complexity (e.g., average desaturation amount, event length, frequency of events, and AHI). It does not have to be just one measure. Five decades have lapsed since the original descriptions of obstructive sleep apnea and the understanding of the pathophysiology and clinical outcomes has improved greatly. However, our ability to characterize OSA severity been stagnant and is need for change.

5

Figure 1: Illustrative tracing a patient with prolonged hyoponeas.

6

REFERENCES

(1) Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet 2014; 383(9918):736-747.

(2) Lugaresi E, Coccagna G, Mantovani M et al. Hypersomnia with periodic breathing: periodic apneas and alveolar hypoventilation during sleep. Bull Physiopathol Respir (Nancy) 1972; 8(5):1103-1113.

(3) Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. Annu Rev Med 1976; 27:465-84.:465-484.

(4) Hudgel DW. "Apnea index": need for improving the description of respiratory variability during sleep. Am Rev Respir Dis 1986; 133(4):708-709.

(5) Gould GA, Whyte KF, Rhind GB et al. The sleep hypopnea syndrome. Am Rev Respir Dis 1988; 137(4):895-898.

(6) Moser NJ, Phillips BA, Berry DT et al. What is hypopnea, anyway? Chest 1994; 105(2):426-428.

(7) Redline S, Sanders M. Hypopnea, a floating metric: implications for prevalence, morbidity estimates, and case finding. Sleep 1997; 20(12):1209-1217.

(8) Ruehland WR, Rochford PD, O'Donoghue FJ et al. The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index. Sleep 2009; 32(2):150-157.

(9) Vijayan VK. Morbidities associated with obstructive sleep apnea. Expert Rev Respir Med 2012; 6(5):557-566.

(10) Mannarino MR, Di FF, Pirro M. Obstructive sleep apnea syndrome. Eur J Intern Med 2012; 23(7):586-593.

(11) Usmani ZA, Chai-Coetzer CL, Antic NA et al. Obstructive sleep apnoea in adults. Postgrad Med J 2013; 89(1049):148-156.

(12) Heatley EM, Harris M, Battersby M et al. Obstructive sleep apnoea in adults: a common chronic condition in need of a comprehensive chronic condition management approach. Sleep Med Rev 2013; 17(5):349-355.

(13) Giles TL, Lasserson TJ, Smith BJ et al. Continuous positive airways pressure for obstructive sleep apnoea in adults. Cochrane Database Syst Rev 2006;(1):CD001106.

(14) Punjabi NM, Newman AB, Young TB et al. Sleep-disordered breathing and cardiovascular disease: an outcome-based definition of hypopneas. Am J Respir Crit Care Med 2008; 177(10):1150-1155.

(15) Stamatakis K, Sanders MH, Caffo B et al. Fasting glycemia in sleep disordered breathing: lowering the threshold on oxyhemoglobin desaturation. Sleep 2008; 31(7):1018-1024.

(16) Shahar E. Apnea-hypopnea index: time to wake up. Nat Sci Sleep 2014; 6:51-56.

7

336x138mm (72 x 72 DPI)

CHEST™

OFFICIAL PUBLICATION OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

ONLINE FIRST

This is an Online First, unedited version of this article. The final, edited version will appear in a numbered issue of *CHEST* and may contain substantive changes. We encourage readers to check back for the final article. Online First papers are indexed in PubMed and by search engines, but the information, including the final title and author list, may be updated on final publication.

http://journal.publications.chestnet.org/

Online First articles are not copyedited prior to posting.

Word count: 561

Rebuttal From Dr. Rapoport

David M. Rapoport, MD
Division of Pulmonary, Critical Care and Sleep Medicine
New York University School of Medicine
NY, NY

Email: david.rapoport@nyumc.org

Address:
     Sleep Disorders Center
     Bellevue Hospital
     462 First Ave. Room 7N2
     New York, NY 10016

In his editorial[1] Dr. Punjabi points out intrinsic limitations of the AHI concept: the cycle rate of events does not capture physiological "severity" of each event (eg, quantitative flow reduction, event duration) or biological impact (eg. degree of desaturation, sympathetic activation); temporal distribution of events is not captured (eg clusters of apnea/hypopnea are counted equally to widely separated individual events); other essential aspects of sleep are ignored (eg total duration of sleep determines overall exposure to sleep disordered breathing). Thus, he argues AHI is an overly simplistic representation of the complex physiology of a 7 hour recording of the polysmonogram.

The above criticisms are numerical tautologies. These conceptual limitations of the AHI as a marker of physiological information cannot be denied in concept and we definitely should explore better metrics to correlate physiologic and clinical outcomes. However, to date (somewhat surprisingly) none of the attempts to "improve on" the AHI have produced improved results. This may change in the future, but an alternative conclusion is that the AHI is as good as anything because "severity" of the physiological process is not the relevant endpoint, as if differential susceptibility plays a role. In the latter case, one can preserve the AHI's utility by restricting its use to two extremes of severity: defining severe disease and identifying "normal" subjects who do not have SDB, Other metrics (as suggested by Dr. Punjabi) can then be explored, but primarily in patients exhibiting the "mid-" region of AHI severity.

This approach refines the approach to SDB by moving away from the idea of a linear spectrum of severity. I propose that the AHI be used in the following way:
1. An "inclusive" (ie very sensitive) AHI, with a relatively low threshold, likely defines individuals who are "normal" – ie without demonstrable health consequences of their upper airway physiology. If forced to give such a definition today pending further research, perhaps <10 events/hr with arousals lies "within normal limits."
2. A different and more restrictively defined AHI that is above a *different* and higher threshold likely identifies individuals with clear SDB. Based on the literature quoted earlier, >30 events/hr with 4% desaturation might be a place to start (today) in defining this group.
3. For those individuals neither normal nor having clear SDB the AHI may be less useful, for the reasons suggested by Dr. Punjabi. For these subjects only (I estimate ~1/3 of those being evaluated for SDB are in this category) I would advocate that either refinements of analysis (eg REM or supine AHI, peak AHI, etc) or entirely new metrics may be needed in research and clinical practice for purposes that are not quite "severity:" ie, to decide which individuals have a sufficiently increased likelihood of consequences that they should be treated; which of these have findings on their polysomnogram that can/cannot be used to explain clinical complaints, in studies of epidemiology; and to evaluate the effect of therapeutic interventions. This search for other metrics, useful only in the "grey" area of AHI severity, should replace the current reliance on clinical symptoms for these subjects.

I believe many thoughtful clinicians follow a similar thought process rather than simply using AHI as a linear metric of severity. What is needed today is not to throw out the AHI entirely, but rather demote it from the level of "gold-standard" as a severity metric and use it rationally.

1. Punjabi, N. Counterpoint: Is the AHI the best way to quantify the severity of sleep disordered breathing – No. Chest. 20XX…..

CHEST™

ONLINE FIRST

This is an Online First, unedited version of this article. The final, edited version will appear in a numbered issue of *CHEST* and may contain substantive changes. We encourage readers to check back for the final article. Online First papers are indexed in PubMed and by search engines, but the information, including the final title and author list, may be updated on final publication.

http://journal.publications.chestnet.org/

Online First articles are not copyedited prior to posting.

Rebuttal From Dr. Punjabi

Naresh M. Punjabi[1,2], MD

Departments of Medicine[1] and Epidemiology[2]
Johns Hopkins University
Baltimore, MD

Word Count: 522

Short Title: Limitations of the apnea-hypopnea index

Corresponding Author:
Naresh M. Punjabi, MD, PhD
Professor of Medicine and Epidemiology
Division of Pulmonary and Critical Care Medicine
Johns Hopkins Asthma and Allergy Center
5501 Hopkins Bayview Circle
Baltimore, Maryland 21224

It is quite reasonable to advocate that the apnea-hypopnea index (AHI) is a clinically valuable metric for obstructive sleep apnea (OSA) on the basis that patients with a high AHI have a higher prevalence of excessive sleepiness, hypertension, and cardiovascular disease compared to those with a lower AHI. Moreover, the contention that the AHI is a "marker of disease" is also sound given that clinical symptoms improve or resolve when the AHI decreases with treatment. However, these arguments only suggest that the AHI is, at best, a crude metric for OSA. Indeed, Dr. Rappaport's conclusion that the AHI is useful in "defining the presence of obstructive sleep apnea if *severely elevated* and … the risk of obstructive sleep apnea is *moderately increased*" indicates that the AHI is not a metric with high fidelity.[1] A high fidelity index of disease can identify the presence of that disease and also exhibit a dose-response association with relevant health outcomes. The lack of a strong association between increasing AHI and clinical consequences, such as daytime sleepiness and hypertension, points to its relative crude nature and rigorous consideration is thus required of alternative or complementary measures that can correlate with endpoints more precisely than the AHI. Furthermore, the fact that the AHI is "most used" is a mere reflection of underlying inertia which is common when an index of disease is adapted early in clinical practice and thus becomes embedded widely. There is absolutely little doubt that part of the challenge in sleep disorders medicine is to understand the heterogeneity in susceptibility to the clinical effects of airway obstruction during sleep. However, that is not a unique phenomenon OSA but a common feature to many chronic disorders. It may well be that unraveling that variability in clinical effects necessitates a better delineation of measures that not only depict the full spectrum of upper airway collapse during sleep but also accurately predict the occurrence of adverse events. The field should not be satisfied with an isolated measure that can just "define" the disorder. It is now time that we look beyond that initial milestone of using the AHI and embrace the complexity of the disorder with better measures that will, in fact, help probe the science of differential susceptibility. There is certainly no scarcity of alternatives. Why not consider additional measures of nocturnal hypoxemia and sleep disruption in characterizing OSA? Perhaps a combination of that include number of sleep disordered breathing events, average oxygen saturation during sleep, frequency of arousals and number of sleep stage transitions can provide a

1

more encompassing view of OSA. Why not quantify the number of flow-limited breaths to delineate the burden of respiratory effort during sleep? Automated methods are now readily available that can easily differentiate flow-limited from non-flow limited breaths from an overnight polysomnogram. Such analyses will help reinvigorate additional research into defining the ramifications of increased work of breathing associated with airway obstruction – an area that remains neglected. If the AHI remains as the "holy grail" in sleep and respiratory medicine, the science will certainly not advance which will, in turn, retard the clinical and public health response to this disease.

References

1. Rapoport, DM. Point: Is the AHI the best way to quantify the severity of sleep disordered breathing – Yes. Chest. 20XX ….