Guilleminault et al. first discovered upper airway resistance syndrome (UARS) in children in 1982. Subsequently, his research teams published many papers on the UARS pathophysiological process in adults; and other research showed similarities between UARS and obstructive sleep apnea (OSA). Several works highlight the daytime impact of UARS on sleepiness and impairment in patients who suffer UARS exclusively. Numerous review articles summarize these findings.

In the 1990s, esophageal manometry was the gold standard tool to measure UARS. Advances in direct measurement of airflow through pneumotachography and pressure transducers offered new ways to assess UARS. One group reported on UARS with the term “flow limitation events” (FLEs). Among some researchers and clinicians, an emerging perspective described UARS as a clinically relevant, integral component of obstructive sleep disordered breathing; but a majority of clinicians and researchers may have been unaware of or unconvinced about its clinical relevance.

In 1999, UARS was first defined in a nosology-related publication as respiratory effort-related arousals (RERAs). Nasal cannula pressure transducer (NCPT) received a passing grade to evaluate RERAs or hypopneas, whereas thermistor/thermocouple devices received a grade of “D” to measure hypopneas and no grade for RERAs. As more UARS papers were published, flow limitation and RERA terms spread; and evidence provided validity for NCPT as a surrogate for esophageal pressure monitoring. With greater use of nasal cannula pressure transducer devices, the AASM recommended this technology as the standard in 2007.

The terms UARS and RERA were formally incorporated into the AASM nosology in 2005 and into the scoring atlas in 2007. The respiratory disturbance index (RDI) was implicitly defined as all breathing events divided by total sleep time. However, AASM published a policy paper in 2007 declaring the scoring of RERAs “optional,” because “RERAs are specific but relatively rare respiratory events in individuals with moderate to severe SRDB.” This consensus statement was based on a single article by Cracowski et al. studying 15 “unselected patients suspected of suffering from UARS or mild to moderate OSAHS” and found RERAs accounted for only 5% of total obstructive breathing events. This citation was reiterated in the 2012 rules for scoring respiratory events; one more citation was added, which indicated a 9% rate of RERAs, or nearly double the original proportion reported.

In contrast to optional RERA scoring, in 2008 the AASM described the necessity for titrating out RERAs: “[PAP] should be increased until the obstructive respiratory events are eliminated...” after which another device may be applied to reach higher pressures toward the same ends.

Thus, a paradox was created that has yet to be resolved. On any sleep study, RERAs (a.k.a. UARS or FLEs) can be optionally scored, yet on titrations these events must not only be treated, but also virtually eliminated to achieve an optimal therapeutic effect. An optimal titration is defined as a decrease in RDI to fewer than 5 events/h during a 15-minute interval at a selected pressure tested during supine REM sleep. This guideline aligns with the seminal work of Condos et al. demonstrating how “rounding of the airflow contour” should equate to normalized breathing. In practice, if one considers standard titration protocols, RERAs must make up some proportion (usually > 50%) of residual breathing events during attempts to optimize PAP pressures, and these events are associated with clinical effects.

This background highlights the conflict between the consensus on optional scoring of RERAs on any sleep study and the guideline to eliminate RERAs on a titration in the process of achieving optimal pressure settings. Technically, the conflict has been influenced by the possibility of variable scoring techniques for RERAs as well as reluctance to adopt UARS conceptualizations; however, most clinicians and researchers may not have anticipated a higher prevalence of RERAs in diverse patient samples compared to works cited that minimize the clinical import of RERAs. Moreover, this issue creates potential for flawed diagnostic impressions in patients with low AHI values whose RDI might be incorrectly scored (e.g., classic OARS) as well as in OSA cases that fail to add the RERA index. Also, there is potential to create misleading clinical impressions about optimal titrations by failing to score or treat RERAs.

With mixed signals in the nosology and practice parameters, we sought to comment on the impact of these conflictual policies by examining usage of AASM terms “RERAs” and “RDI” in the Journal of Clinical Sleep Medicine. We reviewed a large series of the Journal’s publications to assess research
about sleep disordered breathing that included objective data. Articles were reviewed to determine whether RERAs were correctly defined, incorporated into RDI, and described in limitation sections if omitted. Surrogate terms such as “snore arousals” or other “respiratory arousals” appearing in narrative or tabular form indicated awareness of and an attempt to score RERAs; therefore we counted these studies as meeting criteria for RERAs or RDI. Mean percentage of RERAs observed as a proportion of RDI was 38.9% (36 of 93 articles). Of the 611 citations, 302 breathing-related articles were published, of which 219 reported objective data in methods and results sections as well as describing measurement of breathing and breathing event metrics. Limitation sections were searched for acknowledgement of the absence of scored RERAs or calculated RDI according to AASM guidelines. All authors participated in review and re-review of pertinent content. RERA/RDI ratios were calculated for papers that provided data when both terms were clearly measured.

RERA mentions were 16.4% (36 of 219 articles). Of the 36, only 21 papers used formal RERA definitions, whereas 15 articles used surrogate terms. Proper RDI calculation was completed in only 11.4% (25 of 219), indicating some studies scored RERAs but did not factor them into the RDI. Four studies reported RDI but not RERA.

Regarding limitation sections, of 219 relevant articles, 40 used RERA or RDI; but in the remaining 179 papers, the majority (n = 157, 87.7%) failed to acknowledge the lack of RERAs or RDI as a limitation. No trends emerged for greater or lesser usage of terms in the 7-year period.

Table 1 lists 11 publications from the Journal during the review period that included specific data to calculate RERAs as a proportion of RDI. Most publications reported multiple data samples (i.e., diagnostic and treatment), yielding 20 subsamples from which 20 RERA/RDI proportions were calculated. The range of RERA/RDI proportions was 5.7% to 92.2%; the mean RERA/RDI% for these 11 studies was 40.63%, the median was 38.90%, and the weighted average was 50.31%, or roughly 500% to 800% higher than the proportions cited by Redline et al. and Berry et al. to recommend optional scoring of RERAs.

Overall, in 219 published articles with objective data on sleep breathing disorders, we found low rates for scoring RERAs and calculating RDI. Few papers designated omission of these terms as a limitation. While our findings appear predictable for diagnostic PSGs given the optional scoring consensus, the absence of any scoring of RERAs in many treatment studies raises concerns juxtaposed to AASM guidelines to titrate out all breathing events. Moreover, the sparse evidence cited to support optional scoring did not align with 11 research studies (Table 1) conducted by groups that correctly scored RDI on diagnostic and treatment studies. These studies showed a substantial proportion of RERAs manifested within the overall RDI (mean RERA/RDI% = 41% to 50%).

The International Classifications of Sleep Disorders’ RERA/RDI definitions.

### Table 1—Proportion of RERAs manifested within overall RDI

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type*</th>
<th>Group Definition</th>
<th>Sample Size</th>
<th>AHI, Mean(SD)</th>
<th>RDI, Mean(SD)</th>
<th>RERA/RDI Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almeida et al. (2009)</td>
<td>3</td>
<td>Diagnostic</td>
<td>n = 23</td>
<td>36.2(21.7)</td>
<td>47.0(20.6)</td>
<td>23.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment (OAT)</td>
<td></td>
<td>16.5(35.1)</td>
<td>27.0(34.5)</td>
<td>38.9%</td>
</tr>
<tr>
<td>Canapari et al. (2011)</td>
<td>1</td>
<td>Diagnostic</td>
<td>n = 15</td>
<td>6.26(6.77)</td>
<td>8.1(7.33)</td>
<td>22.4%</td>
</tr>
<tr>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Eiseman et al. (2012)</td>
<td>2</td>
<td>Diagnostic</td>
<td>n = 159</td>
<td>9.8</td>
<td>22</td>
<td>55.5%</td>
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<td></td>
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<tr>
<td>Gilmartin et al. (2010)</td>
<td>4</td>
<td>Diagnostic</td>
<td>n = 204</td>
<td>36.0(36.8)</td>
<td>69.8(32.8)</td>
<td>48.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment (PAP)</td>
<td></td>
<td>25.4(59.0)</td>
<td>59.4(33.9)</td>
<td>57.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment (PAP-EERS)</td>
<td></td>
<td>4.1(5.8)</td>
<td>30.7(19.7)</td>
<td>86.6%</td>
</tr>
<tr>
<td>Gingras et al. (2011)</td>
<td>1</td>
<td>Diagnostic</td>
<td>n = 90</td>
<td>13.0(17.1)</td>
<td>19.2(18.1)</td>
<td>32.3%</td>
</tr>
<tr>
<td>Khawaja et al. (2010)</td>
<td>2</td>
<td>Diagnostic</td>
<td>n = 114</td>
<td>11.3(17.3)</td>
<td>23.2(20.5)</td>
<td>51.3%</td>
</tr>
<tr>
<td>Krakow et al. (2008)</td>
<td>3</td>
<td>A. Diagnostic</td>
<td>n = 39</td>
<td>25.5(29.8)</td>
<td>49.3(27.3)</td>
<td>48.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment (PAP)</td>
<td></td>
<td>2.0(3.2)</td>
<td>25.6(20.3)</td>
<td>92.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B. Diagnostic</td>
<td>n = 60</td>
<td>27.2(25.0)</td>
<td>48.9(23.4)</td>
<td>44.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment (PAP)</td>
<td></td>
<td>15.3(17.0)</td>
<td>31.8(16.1)</td>
<td>51.9%</td>
</tr>
<tr>
<td>Masdeu et al. (2011)</td>
<td>3</td>
<td>Diagnostic</td>
<td>n = 14</td>
<td>62.8(34.4)</td>
<td>66.6(33.5)</td>
<td>5.7%</td>
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<tr>
<td>O'Brien et al. (2012)</td>
<td>2</td>
<td>Diagnostic (PSG)</td>
<td>n = 31</td>
<td>5.4(8.5)</td>
<td>6.1(8.6)</td>
<td>11.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnostic (WatchPAT)</td>
<td></td>
<td>7.7(13.4)</td>
<td>11.7(13.4)</td>
<td>34.2%</td>
</tr>
<tr>
<td>Patel et al. (2011)</td>
<td>4</td>
<td>Diagnostic</td>
<td>n = 20</td>
<td>34.0(30)</td>
<td>49(28)</td>
<td>30.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment (NERD)</td>
<td>n = 19†</td>
<td>19.9(26)</td>
<td>27(29)</td>
<td>26.3%</td>
</tr>
<tr>
<td>Somiah et al. (2012)</td>
<td>4</td>
<td>Diagnostic</td>
<td>n = 93</td>
<td>37.3(35.5)</td>
<td>42.8(34.3)</td>
<td>12.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment (PAP)</td>
<td></td>
<td>4.4(5.8)</td>
<td>7.2(5.6)</td>
<td>38.9%</td>
</tr>
</tbody>
</table>

*1 = Clinical; 2 = Diagnostic, 3 = Treatment, 4 = Diagnostic and Treatment. †Krakow et al (2008) compared two groups of patients: Group A (n = 39) completed a PAP Nap; Group B (n = 60) historical control group which did not complete PAP Nap. ‡Patel et al (2011) included only one study group (n = 20), however, one patient was excluded due to inability to complete study, resulting in n = 19 for treatment comparison. OAT, oral appliance therapy; PAP, positive airway pressure; EERS, enhanced expiratory rebreathing space; PAT, peripheral arterial tone; NERD, nasal expiratory resistor device.
on RERAs. Moreover, for sleep specialists, several implications arise by deviating from established procedures used to measure sleep disordered breathing regardless of the potential confound from the variability in identifying and scoring RERAs due to sensor placements, anatomical variations, and recording filter settings.

First, some researchers appeared reluctant to score a RERA by name and used alternative or less obvious criteria, which may conflict with new standards for hypopnea that permit a 30% drop in airflow as the lower limit coupled with an arousal. The field of sleep medicine may be better served by either naming all RERAs as another hypopnea variant or holding to the original 2005 nosology in which apneas plus hypopneas plus RERAs are scored as distinct events to yield the most accurate RDI. Notwithstanding, the pervasive conflation of AHI and RDI terms—pervasive among certain entities (e.g., Medicare and home testing manufacturers)—must cease. The recent update on scoring respiratory events spoke forcefully about the improper usage of the term RDI and its routine misapplication as an AHI equivalent: “The literature is very confusing, with many articles defining RDI as the number of apneas and hypopneas per hour of sleep.”

Second, every titration requires: (a) assessment of RERAs in the fine-tuning process to achieve optimal results or (b) a valid index of residual RERAs and residual RDI following suboptimal titrations to guide therapeutic decisions. Effective titrations continuously increase pressures to convert apneas to hypopneas, then hypopneas to RERAs, and finally RERAs to normal breathing. When optimal PAP settings are not attained, RERAs will likely constitute 90% to 100% of residual breathing events. Yet, sleep technologists must treat and score RERAs on all PAP therapy polysomnograms if we are to achieve optimal titrations and outcomes.

Third, concerns about RERAs are relevant to patient care restricted by Medicare. These beneficiaries are not covered for UARS, albeit no clear policy has emerged on scoring and treating residual RERAs during suboptimal titrations. Beyond conventional arguments that Medicare makes coverage decisions, it is common for insurance coverage determinations to inexorably and unfavorably bleed into clinical care decision-making. For example, when a sleep specialist is confronted with a non-adherent PAP patient who repeatedly shows suboptimal titrations, “rescue” devices may be considered, and some patients report benefits by switching to auto-adjusting units. Objectively, auto-PAP therapy may prove more effective when standard, fixed CPAP does not titrate out residual RERAs or when titrations with increasingly higher pressures (to treat RERAs) lead to expiratory pressure intolerance. What are Medicare coverage policies on such patients? What are the policies of other insurance carriers who deny coverage for RERA-related sleep disordered breathing? This environment may influence sleep specialists to ignore scoring rules and label RERAs as hypopneas for the very good reason of attempting to treat poorly responding patients who suffer residual sleepiness. But such approaches undermine the science supported by the AASM’s position to score and calculate the correct RDI. Regrettably, these idiosyncratic insurance coverage positions may lead some sleep physicians to discount “low AHI/high RDI” disorders, because they are not a covered diagnosis.

In closing, some research has shown a need to include the diagnosis and treatment of the most subtle obstructive breathing events (FLEs, RERAs, UARS). And, because RERAs and RDI are both scientifically validated, the argument for optional scoring seems weak. In our opinion, the field of sleep medicine would benefit from a consistent use of its carefully determined and scorable metrics for the objective evaluation and treatment of sleep disordered breathing.

NOTE

A commentary on this article appears in this issue on page 125.

REFERENCES


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This was not an industry-supported study. Dr. Krakow operates 6 websites providing education and offering products and services for sleep disorder patients; he markets and sells 3 books for sleep disorder patients; he owns and operates a commercial sleep center, and is the president of a non-profit sleep research center which has received support from ConAlma, Respironics, GlaxoSmithKline, and Covidien, as well as grants from other non-profit institutions. He has participated in speaking engagements supported by ResMed and Respironics. The other authors have indicated no financial conflicts of interest.