children with OSA have higher arousal thresholds to a number of respiratory stimuli (such as hypercapnia [2] and inspiratory resistance loading [3]), but not to nonrespiratory stimuli (4), compared with age-matched control subjects.

The arousal threshold changes over the course of normal development, with children having a higher arousal threshold compared with adults (5). However, the study by Eckert and coworkers showing blunted respiratory arousal thresholds in adults with OSA suggests that deficits in arousal are a common pathogenic mechanism for OSA across the age spectrum. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply

From the Authors:

We thank Professor Marcus for her interest in our study (1), and for highlighting these key arousal threshold studies in children with and without obstructive sleep apnea (OSA) (2). Our paper focused on adults. The pathophysiology of OSA in children may be quite different. Nonetheless, comparing potential differences and similarities in the varying causes of OSA between adults and children is of interest. In considering the role of arousal in sleep-disordered breathing pathogenesis across the lifespan, it is noteworthy that termination of obstructive respiratory events are rarely associated with cortical arousal in infants (<10%) (3), occur occasionally in children (<50%) (3, 4), and are present more frequently in adults (~80%) (5). These divergences may reflect differences in arousal mechanisms, neuromuscular responses, or a combination of both. The timing of EEG arousal also often does not precisely coincide with airway opening in OSA (5, 6). Thus, EEG arousals are not required for airway opening in OSA and the upper airway muscles are capable of restoring airflow via noncortical arousal mechanisms, especially in infants.

On average, our data indicate that respiratory arousal thresholds are marginally higher (harder to wake up) in adult patients with OSA than in healthy control subjects, even after at least 3 months of continuous positive airway pressure (CPAP) therapy for more than 4 hours per night (1). However, most patients with OSA have arousal thresholds that are within the normal range after therapy (1, 6). In those who have high arousal thresholds despite CPAP treatment (~25% of the patoents with OSA we studied), OSA is typically very severe (6, 7). Increased arousal thresholds in these patients may be inherent or slowly/incompletely reversible. However, caution is warranted, as current treatments for OSA in both children and adults are often incompletely effective in mitigating sleep-disordered breathing and its consequences, particularly when CPAP compliance is considered. Elevated arousal thresholds in OSA may also be protective via preservation of sleep and facilitation of upper airway muscle activity (8–10). Thus, it is unclear if elevated arousal thresholds in some patients with OSA are a consequence/adaptive response or a contributor to the disorder. This may differ between children and adults. A combined pediatric and adult study using standardized techniques to characterize respiratory and nonrespiratory arousal, ideally longitudinally, would likely be insightful in determining the potential role of high arousal thresholds in OSA pathogenesis.

In contrast, CPAP does not appear to decrease the arousal threshold in patients with OSA with low arousal thresholds, who likely represent at least 30% of the current adult OSA population (6). Thus, while there is a group of patients with OSA in whom arousal thresholds are high, others may have inherently low arousal thresholds.

From a phenotyping perspective, it is essential to consider inter-individual variability in arousal thresholds in OSA. The level of hypercapnia associated with cortical arousal in children with OSA varies widely (from ~53 to ~65 mm Hg [7]), as does the negative esophageal pressure to obstructive respiratory events (approximately −8 to −65 cm H_2O [4]). Similarly, while the existing adult arousal threshold literature primarily includes patients with severe OSA, the degree of negative epiglottic or esophageal pressure required to elicit cortical arousal to respiratory stimuli ranges from −8 to −147 cm H_2O (6). The pathophysiological contribution and consequences of arousal for a patient with OSA who wakes up repetitively at −10 cm H_2O compared with another patient who arouses at highly negative pressures will be quite different. Waking up too easily (a low arousal threshold) is likely to contribute to repetitive respiratory events. Certain sedatives increase the arousal threshold (11, 12) and can promote breathing stability in patients with OSA with a low arousal threshold (12). On the other hand, quite a high arousal threshold may contribute to more severe hypoxemia and its accompanying consequences (6). Ultimately, the arousal threshold

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in combination with key anatomical and other nonanatomical phenotypic traits need to be considered on a per-patient basis to improve our understanding of this heterogeneous disorder. While the pathophysiological heterogeneity of OSA is complex, this observed heterogeneity also provides opportunities to better tailor therapies for patients with OSA (1). ■

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Refractory IgG4-related Lung Disease with Constitutional Symptoms and Severe Inflammation

To the Editor:

Rishi Raj summarized the characteristics of IgG4-related lung disease in an Editorial in the September 1, 2013, issue of the *Journal* (1). What he did not discuss, but might be important, is that although respiratory symptoms have been described in approximately one-half of patients with IgG4-related lung disease, constitutional symptoms have been uncommon (2, 3). We present here three cases of IgG4-related lung disease with apparent constitutional symptoms and severe inflammation. All of them were refractory to usual dose of prednisone.

First is a 47-year-old woman with a history of cough and expectoration for 4 years. There were also intermittent fever and urticaria. Chest computed tomography (CT) scan showed a mass with spiculated margins in the right lower lobe, which was surgically resected in suspicion of lung cancer. Postoperative pathology coincided with IgG4-related lung disease, characterized by lymphoplasmocytic proliferation, active fibrois, obstructive vasculitis, and $IgG4^+$ plasmocytes greater than 50/high-power field (HPF). Two similar masses, one in the right upper lobe and the other in the left lower lobe, occurred 4 months after operation, with elevated erythrocyte sedimentation rate (ESR; 67 mm/h) and C-reactive protein (CRP; 14.8 mg/L), but normal serum IgG4 concentration. Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) showed high standardized uptake values (SUV; SUVmax 11.8) in the two masses and in hilar and mediastinal lymph nodes. She was treated with prednisone 40 mg/day, and the masses became larger during treatment. Methylprednisolone 80 mg/day was then given for 5 days, and then tapered to prednisolone 60 mg/day. Meanwhile, mycophenolate mofetil (500 mg three times per day) was added simultaneously. The masses soon shrank. However, during 1 year follow-up, when prednisolone was tapered to less than 15 mg/day or mycophenolat mofetil was reduced, the masses would enlarge in a short time.

Next is a 36-year-old man with a history of cough for 10 months and intermittent hemoptysis for 4 months. There was also occasional fever, and the patient had a smoking history of 16 pack-years. Laboratory tests showed elevated white blood cell count (WBC; 12.62×10^9/L), ESR (106 mm/h), and CRP (114.3 mg/L). IgG4 was also elevated to 7,490 mg/L. Chest CT scan showed multiple nodules and masses in all sizes and densities, which had high SUVs in FDG-PET. Percutaneous lung biopsy yielded a nonspecific result, and biopsy from video-assisted thoracoscopic surgery showed characteristics of IgG4-related lung disease (lymphoplasmocytic proliferation, $IgG4^+$ plasmocytes $>$ 50/HPF, and $IgG4^+$ / IgG^+ = 46%). He was treated with prednisone 45 mg/day, but there was no improvement in imaging at 1 month follow-up.

The final case is that of a 45-year-old woman with a history of fever, cough, and chest pain for 7 months. Inflammatory markers were apparently elevated (WBC 22.44×10^9/L, PLT 592×10^9/L, ESR 124 mm/h, CRP 237 mg/L). IgG4 was also elevated to 3,970 mg/L. Chest CT scan showed an irregular mass in the upper right lobe with air bronchogram, and SUVmax reached 9.9 in