Obstructive Sleep Apnea and Endothelial Function in School-Aged Nonobese Children
Effect of Adenotonsillectomy

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Background—Obstructive sleep apnea (OSA) in children is associated with cardiovascular morbidity such as systemic and pulmonary hypertension. However, it remains unclear whether endothelial dysfunction occurs in pediatric OSA and whether it is reversible on effective treatment of OSA.

Methods and Results—Consecutive nonobese children (aged 6 to 11 years) who were diagnosed with OSA after overnight polysomnography and control children matched on the basis of age, gender, ethnicity, and body mass index underwent blood draw the next morning for soluble CD40 ligand, asymmetric dimethylarginine (ADMA), and nitrotyrosine levels, as well as 2 iterations of 60-second cuff-occlusion tests for assessment of endothelial function. These tests were repeated 4 to 6 months after adenotonsillectomy. OSA children showed blunted reperfusion kinetics after release of occlusion, which completely normalized in 20 of 26 patients after adenotonsillectomy. All 6 children in whom no improvements occurred had a strong family history of cardiovascular disease (versus 2 of the remaining 20 patients; \( P/H_0.04 \)). Plasma nitrotyrosine and ADMA levels were similar in OSA and control children; however, soluble CD40 ligand levels were higher in OSA children and were reduced after treatment, particularly in those with normalized hyperemic responses.

Conclusions—Postocclusive hyperemia is consistently blunted in children with OSA, and such altered endothelial function is reversible 4 to 6 months after treatment, particularly if a family history of cardiovascular disease is not present. Although no evidence for either nitric oxide–dependent oxidative/nitrosative stress or for the increased presence of the circulating nitric oxide synthase inhibitor ADMA was found in children with OSA, soluble CD40 ligand levels were increased in OSA and reflected the changes in endothelial function after treatment. (Circulation. 2007;116:2307-2314.)

Key Words: sleep ▪ inflammation ▪ nitric oxide ▪ hypoxia ▪ endothelium

Obstructive sleep apnea (OSA) is a prevalent condition that affects up to 3% of all prepubertal children.1 The mechanisms that contribute to the pathophysiology of OSA in children are multiple and include anatomic, craniofacial, and neuromuscular factors.2 Like adults, children with OSA are at higher risk for developing neurobehavioral deficits and cardiovascular sequelae.3,4 In regard to the latter, the cumulative evidence suggests that endothelial dysfunction is causally mediated by OSA in adult patients.5–7 Although altered autonomic function, systemic hypertension, and decreased left ventricular function have been documented in children with OSA,8–10 it remains unclear whether this disorder is associated with altered endothelial function, as might be suggested from the elevations in circulating adhesion molecules in children with OSA.11

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One of the mechanisms implicated in vascular morbidity in adult patients with OSA involves changes in nitric oxide pathways, whereby reduced bioavailability of nitric oxide hampers endothelial function and promotes elevation of systemic blood pressure. Furthermore, increased oxidative stress, as evidenced by elevated nitrotyrosine plasma levels and/or increased levels of the endogenous nitric oxide synthase inhibitor asymmetric dimethylarginine (ADMA), correlates with the degree of endothelial dysfunction in adult OSA patients.12–15

Another marker for endothelium-related activation and dysfunction is soluble CD40 ligand (sCD40L). This protein binds CD40 on the surface of various cell types, such as endothelial cells, and triggers the increased expression of inflammatory mediators, growth factors, and the procoagulant tissue factor. On the occurrence of such binding, sCD40L will shed into the circulation, such that increased levels of sCD40L essentially represent the presence of an increased risk in the context of a variety of cardiovascular disorders.16–18 Furthermore, sCD40L levels were found to be

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increased in a recent cohort of 35 adult patients with OSA and were reduced by implementation of continuous positive airway pressure therapy. Thus, OSA appears to induce a proatherosclerotic state that may be monitored through circulating sCD40L concentrations.

On the basis of the aforementioned considerations, we hypothesized that hyperemic responses (as a surrogate marker for endothelial function) would be altered in nonobese children with OSA and that altered nitric oxide–mediated mechanisms would be involved in this process. In addition, we explored the potential relationships between circulating markers of endothelial dysfunction, as exemplified by sCD40L, and flow-dependent reperfusion responses after the release of a cuff-occlusion maneuver before and after treatment of OSA.

Methods

Subjects

Consecutive prepubertal nonobese children diagnosed with OSA at Kosair Children’s Hospital Sleep Medicine and Apnea Center in Louisville, Ky, were invited to participate. The study was approved by the University of Louisville Human Research Committee, and informed consent was obtained from the legal caretaker of each participant. Assent was also obtained from children if they were >6 years of age.

Inclusion criteria were the presence of OSA according to polysomnographic criteria (see below) and age between 6 and 11 years. In addition, age-, gender-, and race-matched children without snoring who underwent overnight polysomnography in the context of another ongoing research study were also invited to participate in the study.

Exclusion criteria included the presence of overweight or obesity; elevated blood pressure; diabetes or prediabetes; craniofacial, neuromuscular, syndromic, or defined genetic abnormalities; current or previous use of montelukast (in the preceding 6 months); current use of antiinflammatory drugs such as aspirin or ibuprofen; acute upper respiratory tract infection; use of any systemic, intranasal, or inhaled corticosteroids or antibiotics in the past 4 weeks preceding the initial sleep study; and any children who already had undergone adenotonsillectomy in the past. In addition, children receiving antihypertensive medications or other medications were not considered eligible to participate.

The following information was gathered from each participant: age, gender, and ethnicity; use of medications (corticosteroids [nasal, inhaled, and systemic], antihistamines, bronchodilators, antibiotics, and leukotriene modifiers); and presence of comorbidities (asthma, allergic rhinitis and other allergies, attention deficit hyperactivity disorder, or psychiatric condition). A detailed family history of cardiovascular diseases was also obtained and included history of cardiovascular diseases (stroke, myocardial infarction, cardiac arrest, or other cardiovascular illness); presence of hypertension and diabetes, or prediabetes; family history of cardiovascular diseases (stroke, myocardial infarction, cardiac arrest, or other cardiovascular illness); and presence of any history of cardiovascular illness. The diagnosis of OSA was based on the presence of obstructive apnea/hypopnea index >1 per hour of total sleep time.

Children with OSA were referred for surgical removal of enlarged tonsils and adenoids, and 4 to 6 months later, they underwent a second overnight polysomnographic evaluation and endothelial function assessment. Control children repeated endothelial function testing only.

Endothelial Function Tests

Endothelial function was assessed with a modified hyperemic test after cuff-induced occlusion of the brachial artery. A laser Doppler sensor (Perimed AB, Periflux 5000 System integrated with the PF 5050 pressure unit, Järfälla, Sweden) was applied over the volar aspect of the hand at the second-finger distal metacarpal surface, and the hand was gently immobilized. Once cutaneous blood flow over the area was stable, the pressure within an inflatable cuff placed at the elbow and connected to a computer-controlled manometer was raised to 160 to 180 mm Hg for 60 seconds, during which blood flow was reduced to undetectable levels. The computer-controlled cuff was then deflated rapidly to enable consistent deflation times, and hyperemic responses were assessed. The maneuver was repeated twice within 10 minutes, and the average of both maneuvers was computed for subsequent analyses. To image peak regional blood flow responses and time required to return baseline regional blood flow before cuff occlusion were considered as representative of the postocclusion hyperemic response.

Plasma sCD40L, ADMA, and Nitrotyrosine Assays

Fasting blood samples were drawn by venipuncture in the morning immediately after the initial diagnostic sleep study into EDTA-containing tubes. Blood samples were immediately centrifuged and frozen at −80°C until assay.

Plasma levels of sCD40L were assayed with a commercially available ELISA kit (BMS 235, Bender MedSystems GmbH, Vienna, Austria) that has a sensitivity of 7.92 pg/mL and a linearity range of 93% to 97%. The intra-assay and interassay coefficients of
Data Analysis

Data are presented as mean±SE unless otherwise indicated. Paired Student t tests were used to compare presurgical and postsurgical sleep findings. ANOVA for repeated measures and independent r tests were used for comparisons of polysomnographic data, vascular response data, and levels of sCD40L and nitric oxide–related compounds and were followed by post hoc tests as appropriate with multiple-comparison Bonferroni correction. All probability values reported are 2-tailed with statistical significance set at <0.05.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A total of 52 children were recruited initially, and 34 of these completed both the initial and follow-up phases of the experimental protocol. These included 8 control children who did not snore and who exhibited normal polysomnographic studies and 26 children with polysomnographically demonstrated OSA. The 18 children who failed to complete the protocol consisted of 10 with OSA and 8 healthy control children who refused to return for follow-up assessments, and they were similar in all aspects to those who ultimately constituted the study population in the present report. As shown in Table 1, these children were similar with respect to age, gender, ethnicity, and BMI. Table 2 shows the polysom-

| Table 1. Demographic Characteristics of 26 Children With OSA and 8 Control Children |
|--------------------------------------|------------------|-----------------|
|                                      | OSA Children (n=26) | P               |
|                                      | 1. Before T&A | 2. After T&A | 1 vs 2 | 1 vs 3 | 2 vs 3 |
| Age, y                               | 6.8±0.5        | 6.9±0.6        | 7.4±0.7 | NS     | NS     | NS     |
| Gender, female:male                   | 3.5             | 10:16          | 10:16   | NS     | NS     | NS     |
| Black, n (%)                          | 3 (38)          | 35 (30)        | 31 (30) | NS     | NS     | NS     |
| BMI, kg/m²                            | 16.8±0.5        | 17.1±0.6       | 17.0±0.5 | NS     | NS     | NS     |
| sCD40L, pg/mL                         | 5728±635       | 1512±598       | 9866±702 | <0.00001 | <0.003 | <0.0002 |
| ADMA, μmol/L                          | 0.96±0.09      | 1.09±0.15     | ...     | NS     | ...    | ...    |
| Nitrotyrosine, nmol/L                 | 622±123        | 503±174       | ...     | NS     | ...    | ...    |

| T&A indicates tonsillectomy and adenoidectomy. |

| Table 2. Polysomnographic Characteristics in 26 Children With OSA, Before and After Tonsillectomy and Adenoidectomy, and in 8 Control Children |
|--------------------------------------|------------------|-----------------|
|                                      | OSA Children (n=26) | P               |
|                                      | 1. Before T&A | 2. After T&A | 1 vs 2 | 1 vs 3 | 2 vs 3 |
| Sleep latency, min                   | 26.2±18.1      | 15.1±12.6      | 23.3±14.2 | <0.01 | NS     | <0.01 |
| REM latency, min                     | 119.3±28.5     | 112.9±33.9     | 117.5±34.1 | NS     | NS     | NS     |
| TST, h                               | 8.6±0.5        | 8.5±0.4        | 8.3±0.4   | NS     | NS     | NS     |
| Sleep efficiency, %                  | 91.7±5.3       | 89.6±6.2       | 90.60.7±6.1 | NS     | NS     | NS     |
| Stage 1, %                           | 7.1±4.2        | 8.0±5.0        | 8.1±5.2   | NS     | NS     | NS     |
| Stage 2, %                           | 41.9±6.4       | 50.1±7.2       | 43.2±6.8  | <0.05 | NS     | NS     |
| Slow-wave sleep, %                   | 24.8±5.9       | 18.0±6.5       | 23.6±6.7  | <0.01 | NS     | <0.005 |
| REM sleep, %                         | 26.2±4.7       | 14.6±6.8       | 24.7±5.1  | <0.005 | NS     | <0.005 |
| Spontaneous arousal index per hour of TST | 7.8±2.1      | 4.4±4.0        | 6.9±3.8   | <0.01 | NS     | <0.05 |
| Respiratory arousal index per hour of TST | 0.0±0.0      | 4.9±0.6        | 1.8±1.0   | <0.001 | <0.0001 | <0.001 |
| AHI per hour of TST                   | 0.0±0.0        | 11.9±2.2       | 1.9±0.7   | <0.00001 | <0.05 | <0.0001 |
| Al per hour of TST                    | 0.0±0.0        | 3.7±0.5        | 0.2±0.3   | <0.00001 | NS     | <0.0001 |
| Mean SpO₂                            | 97.8±0.8       | 95.1±1.1       | 96.9±1.1  | NS     | NS     | NS     |
| SpO₂ nadir                           | 94.1±0.2       | 79.4±1.8       | 92.9±2.1  | <0.00001 | <0.05 | <0.00001 |
| % TST SpO₂ <90%                       | 0.0±0.0        | 2.7±0.2        | 0.1±0.2   | <0.00001 | NS     | <0.00001 |
| Mean PETCO₂                           | 41.9±0.7       | 49.4±1.8       | 47.1±1.6  | <0.001 | <0.05 | <0.01 |
| %TSTPETCO₂ >50 mm Hg                  | 3.9±0.3        | 34.2±4.7       | 21.7±3.9  | <0.001 | <0.00001 | <0.01 |

T&A indicates tonsillectomy and adenoidectomy; REM, rapid eye movement; TST, total sleep time; AHI, obstructive apnea/hypopnea index; AI, obstructive apnea index; and PETCO₂, end-tidal CO₂ pressure.
nographic characteristics before and after surgery in children with OSA and those of the control subjects. Surgical removal of enlarged adenoids and tonsils in the OSA group was associated with normalization of both sleep structure and gas exchange and respiratory function in the children with OSA (Table 2).

**Endothelial Function**

After release of cuff occlusion, cutaneous blood flow returned to baseline levels within 60 to 80 seconds in 8 control children (mean 69.1±9.7 seconds; Figure 1). Hyperemic responses were significantly slower in the 26 children with OSA (113±11.4 seconds; P<0.0001; Figure 1). No significant correlations emerged between the time required for blood flow to return to baseline and OSA polysomnographic measures. Four to 6 months after adenotonsillectomy, hyperemic responses improved significantly in the OSA group (before versus after adenotonsillectomy, P<0.003) and overall normalization of the vascular responses compared with the 8 control children studied at 6-month follow-up (after adenotonsillectomy versus controls, P=NS). However, dichotomous changes occurred among the 26 children with OSA who were tested before and after treatment. Indeed, although clear improvements emerged in 20 of these children, no significant changes in hyperemic responses occurred in 6 of the 26 children with OSA (before versus after adenotonsillectomy, P=NS; Figure 1). The apnea-hypopnea index, nadir SpO2, and arousal index were similar in the responder and nonresponder groups both before and after OSA treatment. A positive family history of cardiovascular disease was elicited in 1 of the 8 control children, in 2 of the 20 children with OSA who had normalized hyperemic responses after adenotonsillectomy, and in all 6 children whose hyperemic responses failed to recover after adenotonsillectomy (OR 9.0, 95% confidence interval 1.19 to 20.92, P<0.04).

**Nitrotyrosine and ADMA Plasma Levels**

Plasma levels of nitrotyrosine were similar among 50 children with OSA and 22 age-, gender-, race-, and BMI-matched control children (Figure 2). Indeed, nitrotyrosine concentrations were 624±45 nmol/L in OSA and 588±64 nmol/L in controls (P=NS). No significant linear correlation existed between any of the polysomnographic measures and nitrotyrosine concentrations. ADMA morning fasting plasma levels were 0.79±0.20 μmol/L in OSA children (n=46) compared with 0.87±0.19 μmol/L in control children (n=22; P=NS; Figure 3), with no significant linear correlations emerging between ADMA levels and any of the polysomnographic measures.

**sCD40L Plasma Concentrations**

Circulating levels of sCD40L were higher in 20 untreated OSA children (15 128±597 pg/mL) than in 20 control children (5729±653 pg/mL, P<0.00001; Table 1; Figure 4). However, only weak significant linear correlations emerged between sCD40L and apnea/hypopnea index (r² 0.19, P<0.05) and nadir SpO2 (r² 0.20, P<0.03). After
adenotonsillectomy, significant improvements in sCD40L occurred (9866 ± 702 pg/mL, \(P < 0.0002\); Table 1; Figure 4). However, postadenotonsillectomy sCD40L levels remained higher than in control children. Further examination of the individual changes in sCD40L after surgical treatment revealed that of these 20 children with OSA for whom sCD40L levels were available, 8 had either no change or minimal decreases in sCD40L (14 877 ± 1023 pg/mL before adenotonsillectomy compared with 13 239 ± 430 pg/mL, \(P = \text{NS}\); Figure 4). Six of these 8 children were among those patients in whom no improvements in post–cuff-occlusion hyperemic responses occurred after adenotonsillectomy, whereas complete normalization of the hyperemic responses occurred in 2 children who exhibited no significant decreases in their sCD40L circulating levels. Conversely, all 12 children with significant decreases in sCD40L (to within control values) also exhibited recovery of their cuff-occlusion hyperemic responses (\(P < 0.0004\)).

Discussion

The present study shows that endothelial function is frequently altered in snoring children with OSA compared with matched nonsnozing children and that treatment of OSA consisting of surgical removal of hypertrophic tonsils and adenoids is associated with normalization of cuff-occlusion hyperemic responses in a large proportion of those children. However, the presence of a strong family history of ischemic heart disease was significantly associated with persistence of endothelial dysfunction after treatment. Furthermore, although no evidence for increased circulating levels of nitrotyrosine or of the endogenous nitric oxide synthase inhibitor ADMA were found in children with OSA, not only were elevations in morning sCD40L concentrations found in the majority of these children, but this improved with treatment in a pattern closely similar to that of the improvements in reactive hyperemic responses.

Substantial evidence now supports the existence of adverse cardiovascular consequences in children with habitual snoring and sleep-disordered breathing. Indeed, increased surges in sympathetic activity have been reported in children with OSA,\(^8,25,26\) and elevation of arterial blood pressure may also occur,\(^4,9,10\) along with altered left ventricular geometry and contractility.\(^27\) The children included in the present study did not present obvious elevations of arterial blood pressure. However, we did not examine temporal trends in systemic blood pressure using continuous blood pressure measurements during both sleep and wakefulness,\(^4\) such that we cannot exclude with certainty that more subtle alterations in systemic blood pressure may have been present. In adults with OSA, extensive evidence has accumulated to clearly support a mechanistic link between OSA and endothelial dysfunction.\(^5–7,28\) Although we are unaware of previous
studies examining functional aspects of endothelium and the microvasculature in children with OSA, recent findings from our laboratory on the presence of circulating inflammatory markers would support the presence of functional alterations in endothelial function among children with OSA. For example, we have recently reported on the association between elevations of interleukin-6 and high-sensitivity C-reactive protein levels and polysomnographic severity measures for OSA in children,29,30 as well as on their reversibility after treatment of the underlying OSA.31 Similarly, increased levels of circulating adhesion molecules suggestive of platelet-endothelial cell activation emerged in children with OSA, even after correction for the degree of adiposity.32 Taken together, these data would support the possibility that a shift to the right in the hyperemic temporal responses may be present among untreated nonobese OSA patients, and indeed, the present findings confirm such an assumption. However, we also expected that effective treatment of OSA would consistently reverse the endothelial functional alterations. Although such prediction indeed concretized for the majority of patients, this was not the case among those children who reported a strong family history of cardiovascular disease.

The mechanisms underlying such discrepant responses to OSA treatment are unclear given the stringent similarity between the demographic and polysomnographic characteristics of the responders and nonresponders. One possibility involves the interactions between 2 diseases, namely, OSA and cardiovascular disease, whereby the occurrence of OSA during early childhood could trigger the onset of cardiovascular disease, such that despite effective treatment of OSA, continued activity of the mechanisms leading to cardiovascular disease would occur and become manifest in the subset of children with a high genetic susceptibility for atherosclerosis and ischemic heart disease. Evidence to this effect can be derived from rodent models of OSA, in which exposures to intermittent hypoxia during sleep in the postnatal period and in early childhood can lead to sustained baroreflex attenuations during adulthood.32 Furthermore, the presence of a genetic predisposition to systemic hypertension was associated with more prominent elevations in blood pressure after intermittent hypoxia during early childhood.33 Alternatively, OSA during childhood could lead to a more sustained activation of inflammatory pathways and to endothelial activation of atherosclerotic processes in genetically susceptible individuals, whereby sCD40L would reflect the underlying persistence of the endothelial processes brought about by the presence of sleep-disordered breathing. Because the duration of follow-up was relatively short, we are still unclear as to whether these children with persistently abnormal hyperemic responses and elevated sCD40L will improve at later stages. Notwithstanding this, the present findings reinforce not only the concept that systemic inflammation is a constitutive component of OSA but that the magnitude of such inflammatory response will increase the probability for end-organ dysfunction. Indeed, we have recently found that morning levels of circulating tumor necrosis factor-α are correlated primarily with the degree of sleepiness and sleep fragmentation induced by sleep-disordered breathing in children34 and that elevated high-sensitivity C-reactive protein predicted the presence of neurocognitive dysfunction.35 However, other pathways pertaining to the local processes that affect the upper airway rather than systemic processes could also play a role. Indeed, the determinants of lymphadenoid growth in the upper airway in children with OSA are still being debated. Although evidence exists of increased numbers of inflammatory cells within the tonsils and adenoids of children with OSA,36–38 the mechanisms underlying such increases remain unclear and may include mechanical vibration–induced inflammation,39 neurotrophin-neurokinin receptor–substance P–related pathways,40 and likely many other possibilities. The primary aim of adenotonsillectomy, however, is to remove the anatomic impingement of the hypertrophic tissue on airway patency rather than to justify the decision of this surgical intervention with regard to the potential presence of inflammation in the upper airway tissues. As such, although it is impossible to determine under the present circumstances whether the reductions in sCD40L were due to the removal of the adenotonsillar tissue per se or to the resolution of sleep-disordered breathing that followed such surgical intervention, the overall association between sCD40L and endothelial function would point toward a systemic response to OSA rather than one that emanates from a localized inflammatory process in the upper airway.

Some methodological considerations deserve comment. First, we excluded overweight and obese children. Obesity is now viewed as a low-grade systemic inflammatory disorder41,42 and is associated with increased risk for OSA-associated morbidities.43 We anticipate that concurrent obesity in the context of pediatric OSA will enhance the magnitude of the biochemical and functional alterations in endothelial beds, and clearly, this issue merits further exploration. Second, we were unable to study 20 of the 52 children at the 6-month follow-up, such that although no a priori differentiating characteristics were present among those who completed and those who failed to complete the protocol, we cannot exclude the possibility that the relative proportion of responders and nonresponders may differ in larger population-based studies. Third, we were unable to confirm the presence of alterations in nitric oxide biology, as evidenced by the preservation of normal nitrotyrosine levels and ADMA concentrations. The reasons for such negative findings may reside in age-related differences to the response to OSA or, alternatively, may be derived from the fact that OSA disease severity is clearly reduced in the pediatric age range when expressed as any of the standard polysomnographic measures.

In summary, we have shown that nonobese children with OSA are at risk for endothelial dysfunction and that the latter correlates with circulating levels of sCD40L in these children. Furthermore, effective treatment of OSA may not be associated with reversibility of the functional endothelial deficits or with the anticipated reductions in atherogenesis-related plasma markers, particularly in those children who have a strong familial history of ischemic heart disease. Future longitudinal studies may allow for further delineation of
genotype-phenotype interactions in the context of OSA and cardiovascular morbidity.

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**Disclosures**

Dr Gozal is on the national speakers’ bureau of Merck and has received honoraria for lectures. Dr Kheirandish-Gozal is the recipient of an investigator-initiated grant from AstraZeneca Ltd on the use of topical steroids in pediatric sleep apnea. The remaining authors report no conflicts.

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**CLINICAL PERSPECTIVE**

The presence of significant cardiovascular morbidity is now being increasingly recognized among children with obstructive sleep apnea, as evidenced by increased risk for systemic and pulmonary hypertension, as well as altered autonomic system function. We now report in a cohort of nonobese nonhypertensive children with obstructive sleep apnea that endothelial function is consistently altered, as suggested by blunted reperfusion responses after cuff occlusion of the upper extremity, and that such blunting of postocclusive hyperemia correlates with morning plasma levels of soluble CD40 ligand but not with either nitrotyrosine concentrations or those of the nitric oxide endogenous inhibitor asymmetric D-methylarginine. Furthermore, although vascular responses and soluble CD40 ligand normalized in the majority of patients 4 to 6 months after effective treatment with adenotonsillectomy, a small proportion of patients failed to improve despite resolution of their obstructive sleep apnea with surgical treatment. The only discernible difference among these 2 divergent responses was the presence of a strong family history of cardiovascular disease among the nonresponders. Thus, endothelial dysfunction is highly prevalent among otherwise healthy prepubertal children with obstructive sleep apnea, correlates with systemic markers of inflammation, and although usually reversible, may sometimes persist, particularly in the context of high genetic background risk for cardiovascular disease.
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