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Otolaryngology -- Head and Neck Surgery 2011 145: 1030 originally published online 26 August 2011
DOI: 10.1177/0194599811420369

The online version of this article can be found at:
http://oto.sagepub.com/content/145/6/1030

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>> Version of Record - Nov 30, 2011
OnlineFirst Version of Record - Aug 26, 2011

What is This?
Effect of Adenotonsillectomy on Endothelin-1 and C-Reactive Protein Levels in Children with Sleep-Disordered Breathing

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No sponsorships or competing interests have been disclosed for this article.

Abstract

Objective. This study aimed to evaluate the influence of adenotonsillectomy on the plasma concentration of endothelin-1 (ET-1) and C-reactive protein (CRP) in children with sleep-disordered breathing (SDB). The relationship between quality of life and ET-1 levels was also evaluated.

Setting. Tertiary referral center.


Methods. Fasting blood samples for ET-1 and high-sensitivity CRP were drawn preoperatively in all patients and at 3 to 4 months postoperatively. The Obstructive Sleep Apnea–18 (OSA-18) survey and Brouilette symptom score were completed by each child’s parents during the same time periods.

Results. The mean ET-1 level decreased from 3.51 ± 0.93 fmol/mL to 2.67 ± 0.69 fmol/mL postoperatively (P < .01). OSA-18 survey scores and Brouilette symptom scores also decreased in the postoperative period (P < .01). When comparing moderate and severe cases to mild cases according to Brouilette scores, ET-1 levels were significantly higher in moderate and severe cases (P < .01). There was a significant correlation between ET-1 and the OSA-18 survey scale (r = 0.442; P = .001). Although CRP levels decreased from 0.63 ± 1.19 mg/dL to 0.31 ± 0.23 mg/dL postoperatively, this was not statistically significant.

Conclusion. Adenotonsillectomy effectively lowered plasma ET-1 levels in children with SDB and thus may have reduced their related risk for cardiovascular disease. In addition, adenotonsillectomy improved quality of life in this group.

Keywords

sleep-disordered breathing, adenotonsillectomy, endothelin-1, C-reactive protein

Received May 11, 2011; revised July 5, 2011; accepted July 26, 2011.
C-reactive protein (CRP), an important serum marker of inflammation, is synthesized from the liver and regulated by cytokines. Although CRP is a nonspecific marker of inflammation, recent epidemiological studies suggest that CRP is an important risk factor in atherosclerosis and coronary artery disease.\(^\text{12,13}\)

The aim of this study was to evaluate the influence of adenotonsilllectomy on ET-1 and CRP plasma concentration in children with SDB. The primary goal was to investigate the effect of adenotonsillar hypertrophy (ATH) and adenotonsilllectomy on the possible pathogenetic mechanisms (endothelial dysfunction and inflammation) that lead to cardiovascular complications.

**Methods**

After a detailed personal and family history was obtained, all subjects included in the study underwent a complete otorhinolaryngologic examination, otoscopy, and anterior rhinoscopy. Flexible nasopharyngoscopy (if tolerated by the child) or lateral-cervical-graphy was also used to detect adenoid hypertrophy and confirm the surgical treatment decision. Hypertrophy of the tonsils was graded according to the system proposed previously by Brodsky.\(^\text{14}\) Children having both grade 3 or 4 hypertrophied tonsils and hypertrophied adenoids large enough to obstruct the choana partially or completely were recruited for the study. Children with any acute inflammatory disease and to be operated on due to recurrent tonsillitis were excluded according to the study protocol. Additional exclusion criteria included the presence of genetic disorders, cerebral palsy, neuromuscular disease, systemic disease, acute infective processes, and any cardiac or noncardiac disease that may have affected the clinical parameters considered in the present analysis.

Body mass index (BMI) was calculated as weight (kg)/height\(^2\) (m\(^2\)) and age and sex specific BMI z scores were calculated according to the 2008 National Growth Charts.\(^\text{15}\)

Children in the study population were also evaluated for their OSA symptom score using a standard questionnaire proposed by Brouilette et al.\(^\text{16}\)

Written informed consent was obtained from the parents of each child. The study protocol was approved by Haydarpasa Numune Education and Research Hospital Ethical Committee, and the study was performed in accordance with the guidelines of the Declaration of Helsinki.

A preoperative anesthetic evaluation that included routine blood and urinary tests was performed together with a chest x-ray. Curettage adenoidectomy and dissection tonsillectomy were performed under general anesthesia. Fasting blood samples for the biochemical evaluation (including high-sensitivity CRP [hsCRP]) were drawn during the preoperative morning and at 3 to 4 months postoperatively in all patients. Immediately after extracting the blood samples from an antecubital vein into a K\(_2\) EDTA tube, the whole blood was centrifuged, and the serum was deep frozen at −80°C until ET-1 evaluation. An endothelin enzyme-linked immunosorbent assay (ELISA) kit (cat. BI-20052; Biomedica, Vienna, Austria) was used for ET-1 determination. ET-1 measurements of preoperative and postoperative blood samples were conducted at the same time using the same assay.

The Obstructive Sleep Apnea–18 (OSA-18) survey, a valid and reliable discriminative quality-of-life (QOL) measure for children with varying levels of SDB,\(^\text{17}\) was completed by each child’s parents preoperatively and at 3 to 4 months postoperatively. The OSA-18 survey has been shown to possess satisfactory test-retest reliability and internal consistency.\(^\text{18}\) The survey consists of 18 items grouped into 5 domains: sleep disturbance, physical suffering, emotional distress, daytime problems, and caregiver concern. The overall survey score is calculated as the mean of the 18 items, which correlates significantly with the respiratory distress index \((R = 0.43)\) and adenoid size \((R = 0.43).\(^\text{18}\)

Because the OSA-18 is usually used with totals for cutoffs, OSA-18 total score was calculated in addition to OSA-18 overall survey score. The OSA-18 also provides a direct global rating of SDB-related QOL via a 10-point visual analog scale with specific semantic anchors.

The postoperative change in the OSA-18 score and change in ET-1 levels were calculated by subtracting the postoperative value(s) from the preoperative value.

**Statistical Analysis**

The results were analyzed with the NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 Statistical Software (NCSS, Kaysville, Utah) computer program. In addition to standard descriptive statistical calculations (mean and standard deviation), preoperative and postoperative ET-1, OSA-18 survey scores, and the mean global QOL rating were compared via a paired sample test. Preoperative and postoperative CRP levels and the Brouilette symptom score were compared by a Wilcoxon signed-rank test. A Pearson correlation test was used to compare the relationship between the parameters. The statistical significance level was established at \(P < .05\).

**Results**

Thirty-seven children with a diagnosis of upper airway obstruction caused by ATH were included in the study. There were 20 female and 17 male patients. The children were between ages 3 and 13 years (mean age, 6.81 ± 2.94 years). Demographic characteristics of children in the study group are shown in **Table 1**. Surgical procedures included 20 tonsillectomies and adenoidectomies (54%), 15 adenoidectomies only (40.6%), and 2 tonsillectomies only (5.4%).

When the preoperative and postoperative ET-1 and CRP serum levels were compared, a statistically significant decrease in ET-1 levels \((P < .01)\) was found. The mean ET-1 level decreased from 3.51 ± 0.93 fmol/mL to 2.67 ± 0.69 fmol/mL postoperatively. CRP levels decreased from 0.63 ± 1.19 mg/dL to 0.31 ± 0.23 mg/dL postoperatively, but this was not statistically significant (**Table 2**).

All OSA-18 domain scores and the overall survey score (the mean score for all 18 items) decreased significantly in the postoperative evaluations \((P < .01; **Table 3**). Caregiver
concerns, physical suffering, and sleep disturbance were the highest rated domains preoperatively. The mean preoperative and postoperative OSA-18 total scores were 80.87 ± 19.22 and 30.42 ± 8.80, respectively (P < 0.01). The mean Brouilette symptom score was 1.99 ± 1.95 preoperatively, which decreased to –3.81 ± 0.13 postoperatively. The change between them was statistically significant (P < 0.01). According to the OSAS symptom score defined by Brouilette, 7.7%, 73.1%, and 19.2% of the cases in this study were classified as having a low, intermediate, and high probability of OSAS, respectively. In the postoperative period, the mean OSAS symptom score of all cases in the study was classified as a low probability of OSAS. The mean global QOL rating on the OSA-18 was 3.69 ± 2.20 preoperatively, which increased to 9.31 ± 0.88 postoperatively (P < 0.01; Table 4).

Table 1. Demographic Characteristics

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>3</td>
<td>13</td>
<td>6.81</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>13</td>
<td>52</td>
<td>24.76</td>
</tr>
<tr>
<td>Body height, cm</td>
<td>90</td>
<td>160</td>
<td>120.32</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>13.50</td>
<td>21.60</td>
<td>16.23</td>
</tr>
<tr>
<td>BMI z score</td>
<td>–1.86</td>
<td>1.20</td>
<td>–0.18</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index.

Table 2. Comparison of Pre- and Postoperative Endothelin-1 and C-Reactive Protein Levels

<table>
<thead>
<tr>
<th></th>
<th>Preoperative, Mean ± SD</th>
<th>Postoperative, Mean ± SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin-1</td>
<td>3.51 ± 0.93</td>
<td>2.67 ± 0.69</td>
<td>.001</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.63 ± 1.19</td>
<td>0.31 ± 0.23</td>
<td>.349</td>
</tr>
</tbody>
</table>

*aPaired samples test.

*bWilcoxon signed-rank test.

P < .01.

Table 3. Comparison of Obstructive Sleep Apnea–18 Survey Pre- and Postoperative Domain Scores and Overall Survey Score

<table>
<thead>
<tr>
<th></th>
<th>Preoperative, Mean ± SD</th>
<th>Postoperative, Mean ± SD</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disturbance</td>
<td>4.37 ± 1.35</td>
<td>1.47 ± 0.53</td>
<td>.001</td>
</tr>
<tr>
<td>Physical suffering</td>
<td>4.67 ± 0.97</td>
<td>1.47 ± 0.64</td>
<td>.001</td>
</tr>
<tr>
<td>Emotional distress</td>
<td>3.49 ± 1.36</td>
<td>2.66 ± 1.33</td>
<td>.012</td>
</tr>
<tr>
<td>Daytime problems</td>
<td>3.71 ± 1.40</td>
<td>1.92 ± 0.89</td>
<td>.001</td>
</tr>
<tr>
<td>Caregiver concerns</td>
<td>5.00 ± 1.49</td>
<td>1.27 ± 0.45</td>
<td>.001</td>
</tr>
<tr>
<td>Overall survey score</td>
<td>4.49 ± 1.07</td>
<td>1.69 ± 0.49</td>
<td>.001</td>
</tr>
</tbody>
</table>

Responses are graded on ordinal scale, from 1 to 7, with higher numbers indicating poorer quality of life.

*aPaired samples test.

P < .01.

Table 4. Comparison of Pre- and Postoperative Mean Global Quality of Life and Obstructive Sleep Apnea Syndrome (OSAS) Symptom Score Defined by Brouilette

<table>
<thead>
<tr>
<th></th>
<th>Preoperative, Mean ± SD</th>
<th>Postoperative, Mean ± SD</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean global quality of life*a</td>
<td>3.69 ± 2.20</td>
<td>9.31 ± 0.88</td>
<td>.001</td>
</tr>
<tr>
<td>OSAS symptom scoreb</td>
<td>1.99 ± 1.95</td>
<td>–3.81 ± 0.13</td>
<td>.001</td>
</tr>
</tbody>
</table>

*aPaired samples test.

bWilcoxon signed rank test.

P < .01.
There was no statistically significant correlation between the OSA-18 change score and change in ET-1 levels ($P = .05$).

As the preoperative and postoperative groups were homogeneous, all preoperative and postoperative OSA-18 survey scores and ET-1 values were collected as a single group. A correlation analysis between the ET-1 and OSA-18 survey score was performed. There was a significant correlation in a positive direction between ET-1 and the OSA-18 survey scale (ie, as ET-1 values decreased, the OSA-18 survey score decreased; $r = 0.442; P < .01$; Figure 1). When ET-1 levels of moderate and severe cases were compared to mild cases according to the Brouilette score, significantly different ET-1 levels were found ($P < .01$; Figure 2).

**Discussion**

It is well known that ATH is the most common cause of upper airway obstruction in children. Sleep-related upper airway obstruction in children may manifest as obstructive apnea or obstructive hypoventilation. In previous studies, it was shown that OSAS in children due to ATH causes pulmonary hypertension and right ventricle (RV) hypertrophy. Other clinical studies have reported systemic hypertension, subclinical RV dysfunction, and cardiac arrhythmias in patients with ATH. Moreover, it was demonstrated that these cardiac changes may be reversed following surgical intervention by adenotonsillectomy.

Although the mechanisms responsible for an increased risk for cardiovascular events in OSAS have not been fully elucidated, hypoxia, inflammation, obesity, metabolic dysregulation, and sympathetic activation may play a role. Endothelial dysfunction may be another link between OSAS and cardiovascular disease. Normal endothelium regulates vasomotor tone and preserves inflammatory and coagulation homeostasis. These functions are altered in patients with OSAS compared with healthy subjects. The endothelium is a source of several vasoactive mediators. A balance between these mediators, including vasoconstrictive factors, such as the renin-angiotensin-aldosterone system, ET-1, thromboxane, and vasorelaxant factors, such as nitric oxide and prostacyclin, are thought to mediate normal vascular tone, homeostasis, and vascular injury repair and growth.

An alteration in this balance can change the vascular milieu and the architectural and tensile properties of the vasculature, promoting vasoconstriction and impeding endothelium-dependent vasorelaxation.

ET-1 is a potent vasoconstrictor peptide that has mitogenic properties and is ubiquitous in human vascular endothelial cells. Kanagy et al found an increase in both plasma ET-1 and blood pressure in rats exposed to intermittent hypoxia/hypercapnia, similar to what might be seen with sleep apnea. The human studies that assess ET-1 levels in OSAS have yielded conflicting results. Several studies report that patients with OSAS have higher systemic levels of ET-1 than their healthy counterparts and that the levels decrease with continuous positive air pressure therapy (CPAP). Such an increase in levels of this peptide may play a role in the genesis of hypertension in OSAS. However, Grimpen et al and Moller et al did not find an association between OSAS and ET-1 elevation. Notably, in the Grimpen et al study, most of the patients and controls had a history of hypertension and cardiovascular disorders, suggesting the possibility of endothelial dysfunction in both groups and, hence, no significant difference in the ET-1 levels between the 2 groups. Other authors demonstrated elevations of plasma big ET-1 (a precursor of ET-1) levels in untreated OSAS patients, which attenuated with long-term CPAP therapy. In contrast, plasma ET-1 concentrations were within the physiological range in these patients. Finally, a recent study found elevated ET-1 levels in moderate or severe OSAS patients but not in mild OSAS patients. All of these studies were conducted in an adult population. In addition, most of them focused on the influence of CPAP therapy on ET-1 level, not surgical intervention. To our knowledge, there is no study that investigates ET-1 levels in upper airway obstruction due to ATH in
pediatric patients. In our study, postoperative ET-1 levels were significantly lower than preoperative ones. Therefore, we can say that upper airway obstruction due to ATH may cause ET-1 secretion, and adenotonsillectomy may lead to a decrease in ET-1 levels. Several studies have found an association between pulmonary hypertension and SDB due to ATH in children. Hence, we also can claim that ET-1 may have a role in the pathogenesis of pulmonary hypertension in pediatric patients with SDB.

The OSA-18 is the only survey that has been validated as both a discriminative measure of SDB severity among individuals and an evaluative measure of longitudinal change in SDB status. Clinicians and researchers can use the OSA-18 to categorize the baseline impact of SDB on QOL and to quantify changes in QOL over time. In our study, we used both the OSA-18 survey and the OSAS symptom score defined by Brouilette. Both the OSA-18 survey score and OSAS symptom score decreased significantly \((P < .01)\) in the postoperative period, which confirmed the clinical improvement reported by patients’ parents. When we investigated the correlation between the OSA-18 change score and change in ET-1 levels, we did not find a statistically significant correlation. However, when we combined the preoperative and postoperative ET-1 and OSA-18 survey score values and performed correlation analysis, we found a significant correlation in a positive direction between ET-1 and the OSA-18 survey score, which means as ET-1 values decreased, the OSA-18 survey score decreased. In other words, as ET-1 decreased, quality of life increased.

CRP is an important risk factor in atherosclerosis and other cardiovascular diseases.\(^3\) CRP is found within atheromatous plaque, correlates with vascular dysfunction, and promotes the secretion of inflammatory mediators by vascular endothelium. Repeated hypoxia in OSAS patients might induce proinflammatory cytokines such as interleukin-6 and tumor necrosis factor–\(\alpha\), which could elevate CRP. Several studies have reported an increased CRP plasma level in OSAS.\(^12,13,32\) Lee et al\(^32\) found that patients with hSCRP \(\geq 3\) mg/L were more prevalent in the severe OSAS group. The increase of hSCRP correlated fairly with BMI, the apnea/hypopnea index, tonsil size, and the Epworth Sleepiness Scale.\(^32\) A recent study showed that OSAS in children is associated with higher LV mass, early LV diastolic dysfunction, and high CRP levels.\(^13\) However, Guilleminault et al\(^33\) showed no relationship between OSAS and CRP in relatively less obese OSAS patients. In fact, they concluded that only BMI was significantly associated with a high CRP. Similarly, in a study from Chung et al,\(^22\) CRP was not associated with OSAS severity, but BMI and waist-to-hip ratio were identified as significant determinants of CRP.

We conducted our study in children. None of the children in our study group had a BMI that was above the normal range. Although CRP levels in our study decreased from 0.63 \pm 1.9 mg/dL to 0.31 \pm 0.23 mg/dL postoperatively, this was not statistically significant.

The results of our study demonstrated higher ET-1 levels in children with SDB in the preoperative period compared with the postoperative period. Adenotonsillectomy led to a significant decrease in ET-1 levels. This is an important finding, suggesting that the positive influences of adenotonsillectomy on cardiovascular complications of SDB might be modulated by its influence on ET-1. In addition, postoperative CRP levels were found to be lower than preoperative levels. Although the latter finding was not statistically significant, it still may support the positive effect of adenotonsillectomy on inflammation.

The major limitation of our study was the small number of subjects enrolled. However, this is a preliminary study that will be followed by more extensive studies about the influence of adenotonsillectomy on ET-1 levels. Moreover, the measurement of pulmonary arterial pressure and ventricular function and their correlation with ET-1 in the pre- and postoperative periods would be more informative to understand the physiopathology of CV abnormalities due to hypoxia in SDB with ATH. In addition, a comparison of ET-1 levels in children with SDB and normal children could give more information about the role of ATH on ET-1. However, the local ethical committee precluded us from taking blood samples from normal children.

In conclusion, the results of our study indicate that children with SDB who undergo adenotonsillectomy may have a better QOL, and the positive influence of adenotonsillectomy on CV function might be mediated by the decrease in ET-1 levels. Further studies with longer follow-up and a larger population sample are warranted to demonstrate the association between SDB due to ATH and ET-1 levels and to confirm the influence of adenotonsillectomy on ET-1 and CRP levels to prevent CV system damage in children.

**Author Contributions**

Arzu Tatlıpınar, conception and design, drafting the article, data collection, and analysis; Burak Çimen, design, revision; Dursun Duman, design, revision; Erkan Esen, data collection and analysis; Sema K köksal, data collection and analysis; Tanju Gökçeer, editing.

**Disclosures**

Competing interests: None.

Sponsorships: None.

Funding source: None.

**References**


