We acknowledge that heart rate response was not novel to our study but consistent with recent data published by Maeder et al.4 Together, these data demonstrate the effects of OSAS on heart rate response and other key markers of autonomic dysfunction elucidate the pathophysiology of OSAS and may explain the favorable effects of treating sleep-related breathing disorders.5

**Table 1**—Baseline Characteristics of Subjects With and Without OSAS*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 92)</th>
<th>No OSAS (n = 50)</th>
<th>OSAS (n = 42)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>139.9 ± 27</td>
<td>135.2 ± 25</td>
<td>145.3 ± 28</td>
<td>0.07</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>48.6 ± 9.3</td>
<td>47.2 ± 9.1</td>
<td>50.5 ± 9.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Respiratory exchange ratio</td>
<td>1.10 ± 0.07</td>
<td>1.11 ± 0.06</td>
<td>1.09 ± 0.08</td>
<td>0.21</td>
</tr>
<tr>
<td>Oxygen uptake, mL/min</td>
<td>2,714 ± 626</td>
<td>2,852 ± 587</td>
<td>2,357 ± 625</td>
<td>0.01</td>
</tr>
<tr>
<td>Maximum oxygen uptake, mL/kg/min</td>
<td>19.4 ± 4.3</td>
<td>21.1 ± 3.8</td>
<td>17.6 ± 4.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.

**Molecular Mechanisms of Corticosteroid Resistance**

To the Editor:

In a recent issue of CHEST (August 2008), Adcock and Barnes1 presented a very interesting and informative study on the molecular mechanism of glucocorticoid (GC) resistance. As the author stated, understanding in detail the action, and inaction, of GCs may lead to the development of new antiinflammatory drugs that are able to subvert the relative corticosteroid insensitivity that is characteristic of patients with severe asthma and COPD. We want to call attention to the preresceptor metabolism of GCs, another mechanism that may have a role in GC resistance. Within target tissues, cortisol and its inactive metabolite, cortisone, are interconverted through the activity of 11β-hydroxysteroid dehydrogenase (11β-HSD).2 Two 11β-HSD isoforms have been characterized and are expressed in lung tissue and immunity cells. In particular, 11β-HSD1 acts as a ketoreductase by virtue of the intracellular localization within the lumen of the endoplasmic reticulum in proximity to the hexose-phosphate dehydrogenase (H6PD).3 H6PD couples the oxidation of hexose-6-phosphate to the reduction of nicotinamide adenine dinucleotide phosphate (NADPH). It is the generation of NADPH within the endoplasmic reticulum adjacent to 11β-HSD1 that drives its reaction direction. Intracellular GC regeneration by 11β-HSD1 is dependent not just on its steroid substrate, but also on G6P import into the endoplasmic reticulum and H6PD-mediated production of NADPH.

In case of oxidative stress, which is common in patients with severe asthma and COPD, the regeneration of endoplasmic NADPH may be impaired and so may be 11β-HSD1 activity. This mechanism may have a great relevance in GC resistance. Prednisolone and prednisone are substrates for 11β-HSD1, and dexamethasone may also be regenerated by 11β-HSD1.3 The physiologic role of 11β-HSD1 in amplifying the GC signal is evidenced by the fact that GCs themselves increase 11β-HSD1 expression in many cells.4 The induction is indirect and requires new protein synthesis activated by CCAAT/enhancer-binding protein (C/EBP)β. (C/EBP)β is a key mediator of metabolic and inflammatory signaling and mediates the effects of GCs on genes that lack GC binding sites in many cell types, among which are the H441 and A549 lung epithelial cells.5 It is possible that GC enhancement of local innate host defense mechanisms is mediated via (C/EBP)β, in contrast to the antiinflammatory mechanisms of GCs, which are predominantly mediated through interference with nuclear factor-κB and activator protein-1 functions.4 Pharmacologic manipulation of 11β-HSD1 activity might contribute to overcoming GC resistance, and promoting (C/EBP)β functions might permit a reduction of the exacerbation of asthma and COPD, in which infectious organisms serve as triggering factors, avoiding the reduction in antioxidant defenses that is associated with nuclear factor-κB and activator protein-1 repression.5

The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

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