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Inhaled Fluticasone and the Hormonal and Inflammatory Response to Brief Exercise

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ABSTRACT

SCHWINDT, C. D., F. ZALDIVAR, A. ELIAKIM, H.-W. LEU, and D. M. COOPER. Inhaled Fluticasone and the Hormonal and Inflammatory Response to Brief Exercise. *Med. Sci. Sports Exerc.*, Vol. 42, No. 10, pp. 1802–1808, 2010. **Purpose**: Inhaled corticosteroids (ICS) improve symptoms in lung diseases, such as asthma. Initial data suggest that the effects of ICS remain localized in the lung; however, recent studies demonstrate alteration to the peripheral immune system in patients with asthma. We sought to evaluate the effect of ICS on peripheral immune mediators and hypothalamic–pituitary–adrenal axis and their response to exercise in healthy men. **Methods**: Eleven healthy males (18–30 yr old) were placed on 2 wk of fluticasone proprionate (440 μg) twice daily. A 30-min bout of exercise was performed on a cycle ergometer at approximately 70% of peak work rate before and after the start of ICS. Blood was sampled before and after exercise. Cytokines and hypothalamic–pituitary–adrenal axis mediators were measured by ELISA, and fluticasone was measured by liquid chromatography/tandem mass spectrometry. **Results**: After ICS treatment, cortisol and adrenocorticotropin were decreased, and a blunted exercise response was observed for cortisol, adrenocorticotropin, and growth hormone. Peripheral leukocytes and neutrophils were significantly increased in response to exercise in both the untreated and the ICS-treated conditions and at baseline after ICS treatment. Interleukin-6 was elevated with ICS treatment, but the exercise response was blunted. Circulating median fluticasone levels were 0.15 ng·mL^{-1} and were increased to 0.20 ng·mL^{-1} in response to exercise. **Conclusions**: Exercise revealed deficits in growth hormone production after ICS treatment not identified by static markers. Neutrophils were shown to be surrogate markers of the systemic effect of ICS. Exercise significantly increased circulating levels of fluticasone. Exercise challenge tests can be used to assess the physiological effect of exogenous corticosteroids. **Key Words**: EXERTION, INHALED CORTICOSTEROIDS, HPA AXIS, GROWTH HORMONE, NEUTROPHILS

Inhaled corticosteroids (ICS) are recommended as the first line of treatment for asthma by broadly attenuating inflammatory processes and, increasingly, even for patients without asthma with bronchoconstriction associated with a variety of illnesses ranging from common colds (7) to empiric treatment in a myriad of pulmonary disorders (23). Clearly, the use of ICS has benefited many patients by reducing the incidence of wheezing and bronchoconstriction while at the same time limiting the adverse effects of corticosteroids that had been typically seen when these agents were administered systemically. Nonetheless, concerns remain regarding the long-term use of ICS (18), and there is an emerging body of data indicating that, although subtle, standard ICS use can affect systemic hormonal and inflammatory processes (17) and may also affect growth in children (12).

Detecting systemic ICS effects relies on long-term measurements such as growth rates and/or changes in bone mineralization or, alternatively, pharmacological agents that stimulate key elements of the growth hormone (GH)–insulin-like growth factor 1 (IGF-I) axis, the hypothalamic–pituitary–adrenal (HPA) axis, and the neuroadrenergic axes. The traditional approaches are not well suited to assess subtle physiological effects of exogenous corticosteroids, particularly in children. It is now well recognized that brief exercise of sufficient intensity is a powerful, naturally occurring, and transient stimulant of both GH–IGF-I, HPA, and neuroadrenergic functions in adults and children (15,21). We reasoned that a physiologic, naturally occurring challenge such as exercise could prove useful in detecting ICS modification of dynamic, systemic, hormonal and inflammatory responses. To our knowledge, no study on the influence of ICS on HPA or on neuroadrenergic responses to exercise has ever been undertaken.

METHODS

Study population. The University of California–Irvine institutional review board approved this study, and informed written consent was obtained from all participants. Twenty-two adult males aged 18–30 yr were recruited for this study. We included participants who were without known illnesses.

We excluded those with a history of asthma or allergies, use of any medications, and the presence of an upper respiratory infection. Eleven participants were excluded (five because of abnormal pulmonary function testing, two developed upper respiratory infections during the study, and four voluntarily withdrew from the study), leaving 11 participants available for analysis. No adverse effects occurred during the study.

Exercise protocol. Participants reported to the University of California–Irvine Institute for Clinical and Translational Science Applied Physiology–Human Performance Laboratory for three visits on separate days. On visit 1, the participants received a comprehensive physical examination and history to evaluate for the presence of existing disease or disorders. Those who met the inclusion criteria performed a standardized exercise protocol to screen for exercise-induced bronchoconstriction (3), the details of which have been previously published (22).

The participants returned to the laboratory for visit 2 (called the "untreated condition") no earlier than 6 d after visit 1 and performed 30 min of heavy-intensity exercise (4) because circulating cortisol is increased only with exercise of moderate-to-heavy intensity (8). Visit 3 (called "ICS-treated condition") occurred exactly 14 d after the untreated condition. The participants performed the same 30-min exercise protocol as they had for the untreated condition visit.

Medication administration. Flovent HFA (GlaxoSmithKline, Research Triangle Park, NC; Fluticasone; 220 μg) and an AeroChamber, Forest Pharmaceuticals, Inc., St. Louis, MO, for proper medication administration, were distributed at the end of the untreated condition visit with instructions to take two puffs morning and night. We chose this dose because it is the highest recommended dose to control asthma symptoms and prevent attacks. We theorized that we were most likely to observe any hormonal or immune changes at the highest dose. Participants received daily reminder calls and the count on dosimeters noted on return. The acceptable compliance was set at >90% of the doses administered. The dosimeter count on visit 2 was used to determine compliance and was found to be 100% in eight subjects, 96% in one subject, and 93% in two subjects.

Blood sampling and analysis. Blood was sampled from an indwelling catheter 30 min after placement and before the onset of exercise and again at the end of exercise for both the untreated and the ICS-treated condition visits. Blood samples were analyzed in the same batch. ELISA for adrenocorticotropin (ACTH), cortisol, GH, and cytokines were performed using DSL ELISA kits from Beckman Coulter (Brea, CA) as per package insert.

Fluticasone propionate analysis. Fluticasone levels were measured after 2 wk of treatment. Samples were obtained approximately 2–4 h after the morning dose and just before and after the exercise challenge. Plasma concentrations of fluticasone propionate were quantified using solid-phase extraction and high-performance liquid chromatography/tandem mass spectrometry (11) at the College of Pharmacy, Department of Pharmaceutics, University of Florida,

Gainesville, FL. The lower limit of detection for fluticasone propionate was 5 pg·mL^{-1}.

Statistical analysis. All data, except exercise parameters, were analyzed using Wilcoxon signed-rank test and rank-sum test, and presented with median and range (minimum–maximum).

RESULTS

Exercise Response

All 11 participants demonstrated a significant response to 30 min of exercise, with similar increases observed in each condition for HR, work rate, and change in lactate (Fig. 1). There was a significantly greater, albeit small, $\dot{V}O_{2max}$ in the ICS-treated condition (mean $\dot{V}O_{2max}$ of 44.88 and 48.07 mL·kg^{-1}·min^{-1} in the untreated and ICS-treated conditions, respectively; mean change of 0.22 mL·kg^{-1}·min^{-1}, $P = 0.012$).

ACTH

Before exercise (baseline). ACTH was significantly decreased ($P = 0.032$) in the ICS-treated condition (median = 2.57 pg·mL^{-1}, range = 0.02–32.64 pg·mL^{-1}) compared with the untreated condition (median = 7.58 pg·mL^{-1}, range = 4.13–30.2 pg·mL^{-1}) at baseline (Fig. 2A).

Response to exercise. ACTH increased significantly in response to exercise in both the untreated (median change = 25.14 pg·mL^{-1}, range = −11.78 to 162.94 pg·mL^{-1}, $P = 0.014$) and the ICS-treated conditions (median change = 1.83 pg·mL^{-1}, range = −0.96 to 18.54 pg·mL^{-1}, $P = 0.014$), although the magnitude of increase was significantly lower ($P = 0.019$) in the ICS-treated condition (Fig. 2A).

Cortisol

Before exercise (baseline). Cortisol was significantly decreased ($P = 0.007$) in the ICS-treated condition (median = 10.39 μg·dL^{-1}, range = 0.95–53.98 μg·dL^{-1}) compared with the untreated condition (median = 32.48 μg·dL^{-1}, range = 10.18–96.6 μg·dL^{-1}) at baseline (Fig. 2B).
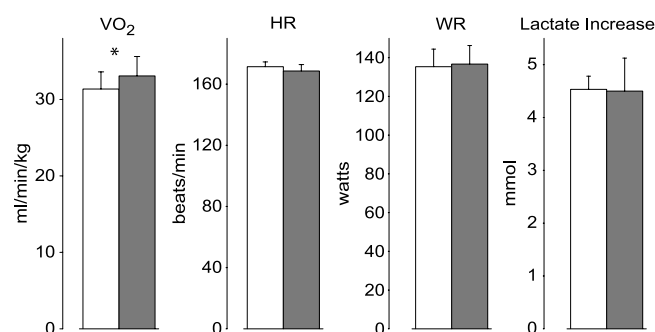

FIGURE 1—The effect of ICS on the exercise response as measured by change in average $\dot{V}O_2$, HR, work rate, and change in lactate in healthy adult male participants. There was no difference between the untreated (*white bar*) and ICS-treated (*black bar*) conditions except for $\dot{V}O_2$ that demonstrated a slight, albeit significant (*$P = 0.012$), increase in the ICS-treated condition.
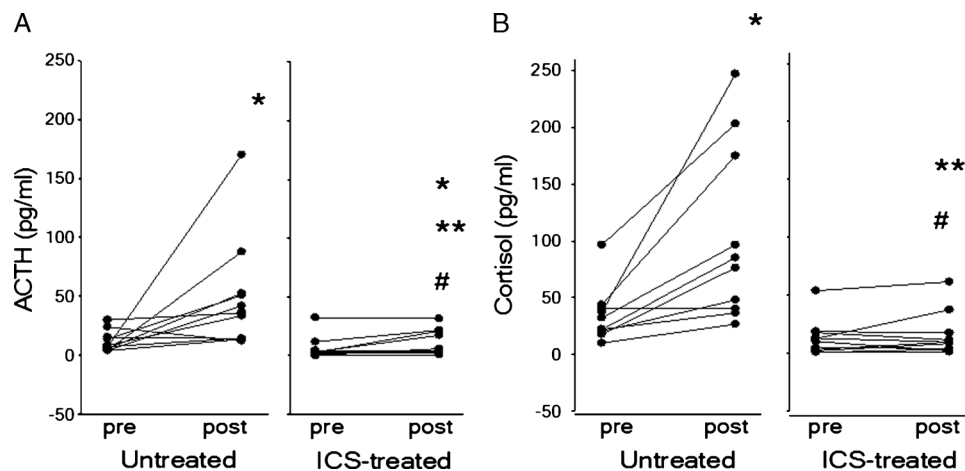
FIGURE 2—The effect of ICS on ACTH and cortisol before and after exercise in healthy adult male participants. Both ACTH and cortisol were significantly lower before exercise ($P = 0.032$ and $P = 0.007$, respectively) in the ICS-treated condition compared with the untreated condition. In response to exercise, ACTH increased significantly in both conditions ($P = 0.014$), although the magnitude of increase was significantly lower ($P = 0.019$) in the ICS-treated condition. Cortisol increased significantly ($P = 0.001$) only in the untreated condition, with a blunted response observed in the ICS-treated condition that was a significant difference ($P = 0.001$) compared with the untreated condition. *Significant exercise response from baseline to peak exercise. **Significant baseline change from untreated to ICS-treated condition. #Significant difference in exercise response between untreated and ICS-treated conditions.

Response to exercise. Cortisol increased significantly in response to exercise in the untreated condition (median increase = 63.03 pg·dL^{-1}, range = 0.07–399.19 pg·dL^{-1}, $P = 0.001$), whereas the exercise response was blunted in the ICS-treated condition (median change = 0.01 pg·dL^{-1}, range = −8.24 to 24.92 pg·dL^{-1}). There was a significant ($P = 0.001$) difference between groups in response to exercise (Fig. 2B).

GH

Before exercise (baseline). GH was detectable (above 0.13 ng·mL^{-1}) in only two participants in both the untreated and the ICS-treated conditions at baseline. Participants whose levels were below detection were assigned 0.01 ng·mL^{-1}. There were no differences at baseline between groups (Fig. 3).

Response to exercise. GH increased significantly in response to exercise in both the untreated (median = 12.73 ng·mL^{-1}, range = 1.41–25.85 ng·mL^{-1}, $P = 0.001$) and the ICS-treated conditions (median = 7.61 ng·mL^{-1}, range = 1.3–16.05 ng·mL^{-1}, $P = 0.002$). The increase in GH in response to exercise in the ICS-treated condition was significantly less than that in the untreated condition ($P = 0.003$; Fig. 3).

Insulin

There were no significant baseline differences between the untreated and the ICS-treated conditions for human insulin. There was also no exercise response for human insulin for either the untreated or the ICS-treated conditions.

Catecholamines

As expected, dopamine, norepinephrine, and epinephrine increased after exercise in both the untreated and the ICS-

treated conditions. There was no difference between the two conditions for catecholamine responses to exercise.

Leukocytes

Before exercise (baseline). The leukocyte count was significantly lower ($P = 0.009$) in the untreated condition (median = 5400 cells per microliter, range = 4300–7500 cells per microliter) compared with the ICS-treated condition (median = 6800 cells per microliter, range = 4800–11,600 cells per
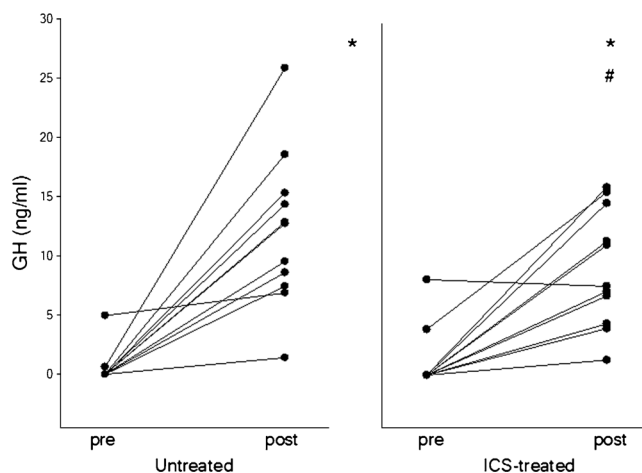

FIGURE 3—The effect of ICS on GH before and after exercise in response to exercise in healthy adult male participants. There was no significant difference between groups before exercise. In response to exercise, GH increased significantly in both the untreated and the ICS-treated conditions ($P = 0.001$ and $P = 0.002$, respectively), but the response in the ICS-treated condition was significantly less ($P = 0.003$) compared with that in the untreated condition. *Significant exercise response from baseline to peak exercise. #Significant difference in exercise response between untreated and ICS-treated conditions.

microliter). Neutrophils were significantly lower ($P = 0.02$) in the untreated condition (median = 2756 cells per microliter, range = 1720–3969 cells per microliter) compared with the ICS-treated condition (median = 4148 cells per microliter, range = 2592–8004 cells per microliter; Fig. 4).

Response to exercise. Exercise increased leukocytes and the key subsets (lymphocytes, monocytes, and neutrophils) in both the untreated and the ICS-treated conditions. The magnitude of the increase was similar in the two conditions, but there was a trend ($P = 0.05$) for a greater increase in the exercise response in the neutrophils in the ICS-treated condition (Fig. 4).

Cytokines

Interleukin-6. *Before exercise (baseline).* Interleukin-6 (IL-6) levels were significantly higher ($P = 0.001$) in the ICS-treated condition (median = 4.88 pg·mL^{-1}, range = 1.64–18.09 pg·mL^{-1}) compared with the untreated condition (median = 1.39 pg·mL^{-1}, range = 0.28–2.81 pg·mL^{-1}). This was a median increase of 2.68 pg·mL^{-1} (range = 0.45–17.82 pg·mL^{-1}) above the untreated condition.

Response to exercise. In response to exercise, the IL-6 levels increased significantly ($P = 0.001$) in the untreated condition, with a median increase of 1.64 pg·mL^{-1} (range = 0.43–4.68 pg·mL^{-1}), which represented a median increase of 85% (range = 36%–416%). Surprisingly, in the ICS-treated condition, we observed a significant decrease in IL-6 ($P = 0.019$), with a median decrease of −1.08 pg·mL^{-1} (range = −12.48 to 4.55 pg·mL^{-1}) and a median percent decrease of 27%.
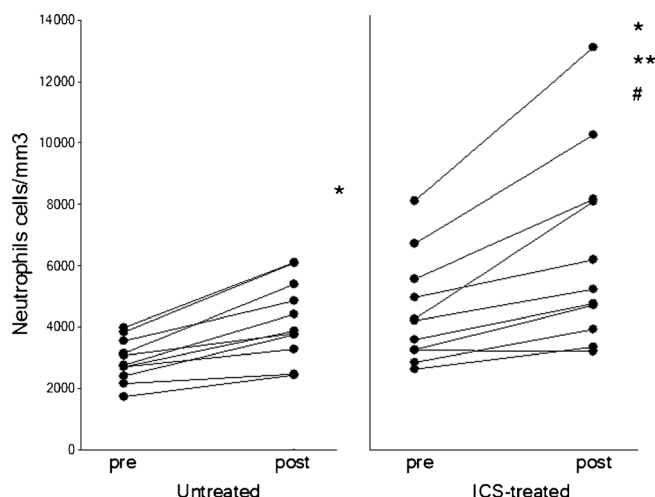
FIGURE 4—Effect of ICS before and after exercise on circulating neutrophils in healthy adult male participants. Neutrophils were significantly increased ($P = 0.02$) in the ICS-treated condition compared with those in the untreated condition before exercise and demonstrated a trend toward a greater exercise response in the ICS-treated condition compared with the untreated condition. *Significant exercise response from baseline to peak exercise. **Significant baseline change from untreated to ICS-treated condition. #Trend ($P = 0.05$) increase in neutrophils in the ICS-treated condition compared with the untreated condition.
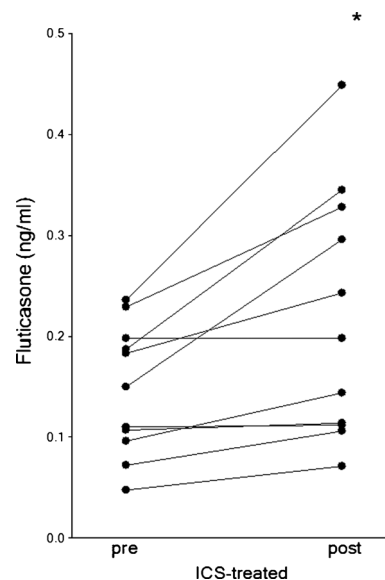
FIGURE 5—Effect of exercise on circulating fluticasone. Fluticasone increased significantly ($P = 0.002$) in response to exercise, with a mean increase of 75% of fluticasone delivered to the peripheral circulation in response to exercise. *Significant increase in circulating fluticasone in response to exercise.

Fluticasone Levels

Fluticasone was measured only in the ICS-treated condition. The median level at baseline was 0.15 ng·mL^{-1} (range = 0.047–0.24 ng·mL^{-1}). Remarkably, we observed a substantial and significant immediate effect of brief exercise on these levels, with a significant increase ($P = 0.002$) to a median level of 0.20 ng·mL^{-1} (range = 0.071–0.45 ng·mL^{-1}). The median increase was 0.05 ng·mL^{-1} (range = 0–0.21 ng·mL^{-1}), which represented a median 50% (range = 0%–97%) increase in fluticasone delivered to the peripheral circulation (Fig. 5). The median percentage change was calculated as the difference between baseline and after exercise divided by the baseline value of fluticasone for each subject.

DISCUSSION

We found a substantial and significant effect of ICS treatment on ACTH and cortisol, key elements of the HPA axis's response to exercise in healthy young men. Consistent with this were also significant effects on GH and the related cytokine IL-6. We observed no effect on the purely neuro-adrenergic hormones, epinephrine, norepinephrine, and dopamine. This is, we believe, the first study to successfully use exercise as a stimulus to test the effect of ICS on key elements of stress and inflammatory mediators. Finally, we noted an unexpected effect of brief exercise on the circulating levels of fluticasone, suggesting a dynamic underlying pharmacokinetic process in which exercise might acutely mobilize depots of the drug stored in the lung or pulmonary circulation.

The pattern of suppression observed in this study, namely, reduced endogenous ACTH, cortisol, and GH with no effect

on catecholamines (epinephrine, norepinephrine, or dopamine) is precisely what would be expected to result from excess parenteral administration of exogenous corticosteroids (1,16,27). Surprisingly, we observed this effect from a recommended, albeit high, dose of ICS. Our findings are in line with a mechanism of suppression also consistent with exogenous steroid use in which fluticasone (which can cross the blood–brain barrier [2]) suppressed the pituitary release of ACTH, leading to reduced ACTH levels in the circulating blood. The lower ACTH, in turn, inadequately stimulated adrenal cortisol production resulting in lower circulating levels of cortisol. The clinical implication of low ACTH and cortisol levels is often questioned, in particular by clinicians, because there are wide-ranging fluctuations in normal levels. However, in this study, we demonstrated a deficient physiological response to exercise in which we observed suppression of the normal increase in ACTH (the mechanism of which is not completely understood [9]) and cortisol in response to exercise. Thus, exercise challenges may prove to be useful in determining the physiological effect of low hormone values when wide-ranging fluctuations in normal values make the clinical effect unclear.

GH release was also suppressed, again, an expected finding because pituitary GH release is inhibited by excessive glucocorticoids. As in previous studies of corticosteroid-blunted exercise responses, we found that the neuroadrenergic (epinephrine, norepinephrine, and dopamine) response to exercise was virtually unaffected by exogenous corticosteroids, as shown in Figure 1. Thus, our observed findings of ICS suppression of the GH response to exercise without changes in catecholamines are consistent with a systemic effect of ICS.

Physicians in general and pediatricians in particular are obviously concerned about the long-term use of ICS, especially in growing children. Recent evidence has suggested that all currently available ICS are absorbed into the systemic circulation and hence have the potential to cause adverse systemic effects (29). Indeed, in a study by Martin et al. (13), sequentially increasing doses of six different ICS, even at low doses, was noted to cause circulating cortisol to sequentially decrease. The clinical implication of this, however, is difficult to assess, especially given the wide-ranging physiological fluctuations in normal values for cortisol and without assessment of the stress response *per se*. In our study, the differences between the untreated and ICS-treated conditions for ACTH, cortisol, and, in particular, GH were only made evident when evaluating the physiological response.

It is well known that the use of systemic glucocorticoids leads to reduction in height, whereas treatment of asthma with ICS can reduce growth velocity (24,28). There is now evidence that ICS may also decrease height as well. In a study by Strunk et al. (26), females were found to have significantly lower height 4.8 yr after the initial Childhood Asthma Management Program study was completed. Thus, adult height may be affected, at least in females. It is believed that the mechanism for the reduced growth velocity does not involve impairment of GH secretion because patients with asthma treated with ICS have normal GH and IGF-I levels (5). The results of the present study suggest that, although there were no effects of ICS on baseline GH levels, exercise-induced GH secretion was attenuated, indicating at least stress-related inhibitory effects on the GH axis.

Increasingly, adverse systemic effects from ICS have been recognized, and they include adrenal suppression, reduced bone mineral density, and an increase in fractures, cataracts, and bruising (6). Despite many reports that ICS are metabolized on first pass through the liver (20), Winkler et al. (29) report that all of the drug that is deposited in the lung will be absorbed systemically and that the main determinant of systemic bioavailability after inhalation is direct absorption from the lung, where, for the currently available ICS, there is no first-pass effect. The percentage of the dose that is deposited in the lung, however, is greatly influenced by the airway caliber (14), which adds credence to recent evidence suggesting that the systemic effects of ICS may differ depending on the underlying inflammation. There is also evidence that the regulation of stress and inflammation may be different in patients with asthma, and thus, the fate of ICS may differ.

There is now a growing body of evidence demonstrating that patients with asthma with chronic inflammation who are *not* treated with ICS are likely to have an attenuated activity and/or responsiveness of their HPA axis. In line with this concept, when the inflammatory response is properly treated with ICS, and the chronic endogenous stress response normalizes, the HPA response also normalizes, with few patients experiencing further deterioration of adrenal function, a phenomenon that may be genetically determined (17,19). The clinical consequences of ICS on static measures of the HPA axis are therefore not clear.

ICS treatment led to a decrease in IL-6 in response to exercise. This is in line with previous reports of the response of IL-6 to acute corticosteroid treatment before exercise (16). An enigmatic finding was the increase in IL-6 at baseline in the ICS-treated condition. The biological significance of this is not yet known.

Cortisol suppression with the use of ICS has previously been described as being accompanied by decreases in lymphocytes and increases in the total white blood cell count and neutrophils (10). We also observed a significant increase in the total white blood cell and neutrophils in the ICS-treated condition, although we did not see a significant change in lymphocytes. The significant increase in neutrophils observed in the ICS-treated condition may be due to the inhibited apoptosis from steroids, which has previously been described with fluticasone (31). Lymphocytes (30) and neutrophils (10) have both been described as being sensitive surrogate markers of the systemic effect of ICS therapy because they change earlier than eosinophils or even cortisol. Interestingly, although we observed a significant decrease in cortisol, we did not observe a significant increase in lymphocytes. Thus, our study suggests that neutrophils may be a more sensitive surrogate marker of the systemic effect of ICS.

In the ICS-treated condition, the median fluticasone level before exercise was 0.15 ng·mL^{-1}. Remarkably, we observed a substantial and significant immediate effect of brief exercise on these levels with a significant increase ($P = 0.002$) to a median level of 0.20 ng·mL^{-1}. Although hemoconcentration may contribute to the increase observed with exercise (8), we observed a 75% increase in fluticasone delivered to the peripheral circulation, which, per package insert, is the equivalent of one puff of 44 μg of fluticasone, far greater than the few percentage points increase that might have occurred due to circulating water volume shifts associated with exercise (25). This finding suggests that a dynamic underlying pharmacokinetic process exists in which exercise might mobilize depots of the drug stored in the lung or pulmonary circulation. This raises an important issue of the overall dose of ICS and the timing of their use in patients with asthma who exercise regularly and, consequently, on their possible adverse effects.

Limitations of this study include the use of one study group; healthy adult males compared with adult males with asthma may have revealed a different stress/inflammatory response to ICS in the presence of inflammatory lung disease, as suggested by Priftis et al. (17). Although different exercise modes and intensities may also have revealed different stress/inflammatory responses, our decision to use a protocol with high intensity was to evaluate the stress/inflammatory system under high stress to identify deficiencies that may only be revealed when maximum stress limits of an organism are reached. Further, an alternate and, perhaps, optimal study design would have been a crossover randomized design with double-dummy–blinded placebo inhalers; however, as a primary research question of ours was of the exercise response to ICS, we decided to use the subjects as their own controls. In addition, our use of one concentration of fluticasone at the highest recommended dose (880 μg·d^{-1}), also to evaluate the response of a maximal dose, prohibited our ability to see the effect of low and moderate concentrations of fluticasone. Evaluating lower, serially increasing concentrations within the range of standard recommended doses would have provided further insight into dose–mechanistic responses of the stress/inflammatory response.

The best clinical practice for the assessment of ICS effects has not yet been defined. Traditional assessment approaches are not well suited to evaluate subtle, physiological effects of exogenous corticosteroids on a dynamic system, particularly in growing children. Exercise challenge tests may prove useful in assessing subtle, physiological effects of exogenous corticosteroids.

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