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# Impaired adrenergic- and corticotropic-axis outflow during exercise in chronic obstructive pulmonary disease

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ABSTRACT

Exercise stimulates coordinated release of the sympathoadrenal hormones adrenocorticotropic hormone (ACTH), cortisol, norepinephrine (NE), and epinephrine (Epi). The study hypothesis was that chronic obstructive pulmonary disease (COPD) is marked by heightened sympathoadrenal outflow at comparable relative workloads. The location of the study was at a clinical research unit. Eight healthy men and 9 men with stable COPD (forced expiratory volume at 1 second <75% predicted) were studied. Volunteers rested (baseline) or exercised at individual submaximal (35% ± 5%) or maximal oxygen consumption. Blood was sampled every 2 minutes for 40 minutes concurrently. Two-way analysis of covariance was applied to examine group (healthy/COPD) and exercise (3 levels) effects on ACTH, cortisol, NE, and Epi release and regularity (estimable by approximate entropy). The timing of peak hormone concentrations was Epi, 14 minutes; NE, 16 minutes; ACTH, 22 minutes; and cortisol, 34 minutes in both cohorts. Type of exercise regimen influenced all 4 hormones (each $P < .001$), and subject group (control vs COPD) affected cortisol ($P < .001$) and Epi ($P = .048$) responses. Exercise regimen and group together controlled ACTH, cortisol, and Epi (each $P < .001$), but not NE, responses. In particular, endocrine responses were attenuated in COPD compared with control subjects. Approximate entropy analysis also identified loss of maximal exercise-induced ACTH-secretory regularity in COPD patients ($P = .042$). These outcomes demonstrate impaired rather than augmented exercise-associated sympathocorticotropic-axis outflow in patients with COPD even when outcomes are normalized to maximal oxygen consumption, suggesting that factors other than fitness are at work.



## 1. Introduction

Exercise stimulates sympathoadrenal outflow, namely, secretion of stress-adaptive noradrenergic (norepinephrine [NE]), adrenal medullary (epinephrine [Epi]), corticotropic (adrenocorticotropic hormone [ACTH]), and adrenal (cortisol) signals [1,2]. The majority of exercise-related endocrine studies have been performed in healthy volunteers rather than in patients with organ-system pathophysiology. In fact, the impact of catabolic illnesses like chronic obstructive pulmonary disease

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(COPD) on corticotropin secretion is not well studied. Higher basal sympathetic neural activity, reduced glycolytic muscle fibers, (severe) hypoxia-induced ACTH but not cortisol elevation, cachexia, and relative tissue resistance to insulin and growth hormone have been suggested in COPD [3-5]. A major clinical implication of these findings is that stress-evoked sympathoadrenal outflow, if excessive, could exacerbate morbidity due to accentuated vasoreactivity (NE), glucose intolerance (Epi and cortisol), muscle wasting (cortisol), and hypertension (NE, Epi, cortisol).

Chronic catabolic processes, such as COPD, are often associated with elevated systemic concentrations of certain inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor–α [6]. Cytokines constitute major stimuli of corticotrope-adrenal secretion [7]. Low physical fitness, a characteristic of COPD, likewise predicts greater responsiveness of β-endorphin, ACTH, cortisol, and Epi to an exercise stimulus [8]. Greater hypoxia and/or dyspnea (perceived respiratory distress) could be expected to potentiate ACTH-cortisol secretion at equal power output [9,10]. Conversely, reduced renin-angiotensin activity, also reported in COPD [11], might attenuate stress-induced ACTH and cortisol secretion [12]. These predictions follow from studies in healthy volunteers with normal baseline pulmonary function. To our knowledge, no comparable data exist in patients with stable COPD not receiving glucocorticoids. We hypothesized that COPD is marked by excessive exercise-associated ACTH, cortisol, NE, and Epi outflow during maximal voluntary exertion.

## 2. Methods

### 2.1. Subjects

The study was reviewed and approved by the Human Investigation Committee of the Veterans Affairs Medical Center, Salem, VA. Written informed consent was given by all subjects. The study sample comprised 8 healthy men ($FEV_1$ >75%) and 9 ambulatory male patients with documented stable (2-8 years) COPD (forced expiratory volume in 1 second [$FEV_1$] <75%), unchanged weight over 3 months, the absence of cor pulmonale, and no exposure to glucocorticoids within 3 months. Volunteers with angina pectoris, congestive heart failure, arrhythmia, blood pressure greater than 200/120 or lower than 90/60 mm Hg, any acute illness, acute or chronic pain, narcotic or progestin exposure, impaired mentation, balance disturbance, or orthopedic compromise were excluded. Anemia, recent transfusion, anabolic steroid use, pituitary disease, $FEV_1$ less than 15%, and history of syncope or hypotension were exclusion criteria also. Other subject characteristics are summarized in Table 1.

**Table 1 – Baseline subject characteristics**

| Variable | Healthy (n = 8) | COPD (n = 9) | P value |
|---|---|---|---|
| Age (y) | 53 ± 2.5 | 65 ± 4.3 | NS |
| BMI (kg/m$^2$) | 28 ± 0.63 | 24 ± 1.1 | <.010 |
| Peak flow (L/min) | 4.7 ± 0.14 | 1.3 ± 0.20 | <.001 |
| $FEV_1$ (% predicted) | 93 ± 4.4 | 43 ± 6.4 | <.001 |
| NE baseline (nmol/L) | 2.8 ± 0.22 | 3.2 ± 0.36 | NS |
| Epi baseline (nmol/L) | 0.33 ± 0.052 | 0.44 ± 0.098 | NS |
| ACTH baseline (pmol/L) | 6.6 ± 1.4 | 6.2 ± 2.9 | NS |
| Cortisol baseline (nmol/L) | 364 ± 48 | 280 ± 53 | NS |

Data are the mean ± SEM. NS denotes $P \geq .01$. Baseline, mean of 40 resting samples in each subject.

### 2.2. Protocol

Subjects were studied on 4 separate days always at least 72 hours apart. Subjects with COPD and controls exercised and rested in the same order of sessions. The first day was always a practice session without blood sampling to allow estimation of individual maximal exercise-associated heart rate (HR), oxygen consumption ($V_{O_2}$), and dyspnea score. The second entailed maximal voluntary exercise with 2-minute sampling for 40 minutes. On the third day, participants remained seated and resting while sampled. The fourth day comprised submaximal exercise defined by 35% ± 5% of maximal $V_{O_2}$ ($V_{O_{2max}}$) with venous sampling every 2 minutes for 40 minutes. Thus, the second and fourth days of study were at least 144 hours apart.

Volunteers performed bicycle ergometry (SensorMedics Exercise Test Analyzer, Yorba Linda, CA, USA) incremented in a continuous ramp fashion by 10 to 25 W/min. Participants initially rested on the bicycle for 5 minutes. At time zero, subjects began to pedal with no load for 4 minutes and then against increasing load for up to 15 minutes or until symptoms of limiting breathlessness or fatigue intervened. Dyspnea was quantified using the modified Borg score [13], in which exercising subjects pointed every 2 minutes to a card marked with numbers ranging from 0 for no dyspnea to 10 for extreme dyspnea. Heart rate, minute ventilation (VE), and $V_{O_2}$ were monitored every 20 seconds; and blood pressure and arterial oxyhemoglobin saturation (by pulse oximetry), every 2 minutes.

No subject experienced any untoward event during the exercise phases of the protocol. Two healthy men had transient hypotension and dizziness without syncope in the recovery phase of the protocol.

### 2.3. Borg dyspnea score (perceived exertion) and catecholamine thresholds

Baseline dyspnea scores were obtained during unloaded pedaling. The *time-dyspnea threshold* was defined as the time at which the Borg estimate departed exponentially from mean baseline. The same concept was applied for NE and Epi thresholds. Borg scores were also regressed against $V_{O_2}$, expressed as a percentage of observed individual maximal $V_{O_2}$. The *$V_{O_2}$-dyspnea threshold* was defined as $V_{O_2}$ when the Borg estimate deviated from baseline.

### 2.4. Sampling

After the subject arrived in the laboratory on the exercise test day, an intravenous catheter was inserted into each forearm. Blood samples (3 mL) were withdrawn beginning with the

onset of unloaded pedaling (time 0) every 2 minutes as plasma in chilled plastic tubes with EDTA, yielding a total of 20 samples per session.

### 2.5. Hormone assays

Plasma NE and Epi concentrations were measured by radioimmunoassay (RIA) using the KatCombi RIA kit (ALPCO, Windham, NH), which includes an affinity-extraction step performed on a macrotiter plate. Intra- and interassay coefficients of variation were 8.5% and 11.2%, respectively. Plasma ACTH and cortisol concentrations were measured in duplicate in each 2-minute sample using a robotics-automated 2-site immunoradiometric assay and solid-phase RIA, respectively [14,15]. Median within-assay coefficients of variation were 8% and 5%; and sensitivities were 1.1 pmol/L and 38.8 nmol/L, respectively. No sample had undetectable measurements of any hormone.

### 2.6. Analyses by deconvolution and approximate entropy

Norepinephrine, Epi, ACTH, and cortisol time series were subjected to deconvolution and approximate entropy (ApEn) analyses. The deconvolution method was described in Kennan et al [16], except that only a single secretory-burst waveform was allowed. The framework is a maximum-likelihood model [17] with the additional threshold requirement that valid hormone-concentration peaks reduce the Akaike information criterion by $P < .05$. Outcomes for ACTH were ACTH secretory-burst mass (picomoles per liter) and number (per 40 minutes), pulsatile and nonpulsatile (basal) ACTH secretion (picomoles per liter per 40 minutes), ACTH half-life (minutes), and secretory-burst shape (mode or time delay to maximal secretion in minutes). Catecholamine and cortisol units were nanomoles per liter. Sensitivity and specificity of pulse detection both exceed 92.5% with this methodology [18].

The ApEn statistic was used to discriminate changes in secretory regularity as a barometer of altered feedback state during exercise [19]. The ApEn quantifies the relative orderliness or subpattern consistency in a time series, with higher ApEn corresponding to less regularity (greater randomness). The cross-ApEn by analogy quantifies the relative synchrony (joint regularity) of subpatterns in paired time series. Higher cross-ApEn denotes less synchrony (greater asynchrony). The terms *feedforward* and *feedback cross-ApEn* refer to ACTH-cortisol and cortisol-ACTH linkages, respectively, as defined earlier [20] and analogously for NE-Epi and Epi-NE pairs.

### 2.7. Statistical analysis

Because each subject had a baseline resting session of identical 2-minute sampling, analysis of covariance (ANCOVA) was used to adjust for intraindividual correlations among baseline, low-exercise, and maximal-exercise responses. The covariate was the subject's parameter value on the baseline day. The model structure comprised hierarchical mixed-effects 2-way ANCOVA with 3 exercise levels (resting, low exercise, and maximal exercise) and 2 specification parameters (diagnostic subject groups: healthy controls and COPD patients) [21]. Logarithmic transformation was used to limit heterogeneity of variance. The equal-slopes assumption of the ANCOVA structure was verified by a generalized F ratio test, followed by restricted maximum-likelihood estimation of parameters. Rejection of prespecified hypotheses was based on a multiple-comparison experiment-wise type I error rate of less than 0.05 using the Tukey honestly significantly different post hoc test.

### 2.8. Data presentation

Values are given as the mean ± SEM. Differences in baseline characteristics (eg, age, body mass index [BMI]) values between healthy subjects and COPD patients were evaluated using an unpaired 2-tailed Student *t* test at a protected critical value of $P \leq .01$, given that 8 comparisons were required [22].

## 3. Results

### 3.1. Characteristics of subjects

Patients with COPD were nonsignificantly older and had significantly lower BMI than control subjects (Table 1). Forced expiratory volume in 1 second ranged from 79% to 114% predicted in healthy men and from 17% to 73% in COPD patients ($P < .001$). Mean baseline (resting) plasma ACTH, cortisol, NE, and Epi concentrations did not differ by group.

### 3.2. Threshold values

The times (minutes) at which Borg-dyspnea (perceived exertion) scores departed from baseline (thresholds) overlapped in healthy subjects (6.6 ± 1.9) and COPD patients (5.0 ± 1.0). One-half maximal dyspnea occurred after 9.8 ± 1.1 (healthy) and 8.1 ± 1.6 (COPD) minutes ($P < .05$). The respective threshold times for NE and Epi rises were also comparable in healthy subjects (11 ± 1.9 and 12 ± 1.1 minutes) and COPD patients (9 ± 2.4 and 12 ± 1.4 minutes). The NE and Epi thresholds occurred significantly later than the Borg dyspnea-score thresholds in both groups ($P < .01$).

The $V_{O_2}$ thresholds (percentage of $V_{O_{2max}}$) for Borg dyspnea score, NE, and Epi elevations were 23 ± 5, 56 ± 10, and 60 ± 10 in healthy men and 34 ± 6, 60 ± 9, and 60 ± 9 in COPD patients. Only the Borg-dyspnea $V_{O_2}$ thresholds differed in the 2 study groups by being higher in COPD ($P < .001$).

### 3.3. Maximal-exercise performance

Healthy subjects achieved significantly higher maximal values of VE, HR, and $V_{O_2}$ than COPD patients (Table 2), thus verifying fitness differences. Percentage maximal $V_{O_2}$, expressed as a percentage of the predicted $V_{O_{2max}}$, did not differ, namely, 85% ± 13% in healthy subjects and 70% ± 19% in COPD patients ($P$ = not significant). To illustrate functional differences, at an absolute $V_{O_2}$ of 9.8 ± 3.3 mL/(kg min), the Borg score was 4.0 ± 2.9 in COPD vs 1.3 ± 1.1 in healthy subjects ($P < .01$).

Fig. 1 depicts (mean ± SEM) hormone concentration profiles over time in the 2 groups (healthy and COPD) for each of the 3 exercise levels (none, submaximal, and

**Table 2 – Performance at maximal exercise**

| Variable | Healthy (n = 8) | COPD (n = 9) | P value |
|---|---|---|---|
| VE at end exercise (mL/[kg min]) | 72 ± 14 | 39 ± 13 | <.001 |
| VE (% predicted maximum) | 49 ± 11 | 77 ± 20 | <.001 |
| $HR_{max}$ (beat/min) | 161 ± 14 | 133 ± 13 | <.001 |
| HR (% predicted maximum) | 96 ± 6.0 | 86 ± 7.0 | <.010 |
| $Vo_{2max}$ (mL/[kg min]) | 27 ± 4.3 | 17 ± 4.0 | <.001 |
| $Vo_2$ (% predicted maximum) | 85 ± 13 | 70 ± 19 | NS |

Data are the mean ± SEM. NS denotes $P \geq .01$.

maximal) and for each of the 4 hormones (ACTH, cortisol, Epi, and NE). Healthy subjects, but not COPD patients, manifested distinct hormone peaks during maximal exercise at 14 minutes (Epi), 16 minutes (NE), 22 minutes (ACTH), and 34 minutes (cortisol). Results of ANCOVA of the 6 time series in each panel are given, showing group contrasts for cortisol ($P < .001$) and Epi ($P = .048$) and a similar trend for ACTH ($P = .094$). Exercise regimen was a significant factor for all 4 of ACTH, cortisol, Epi, and NE responses (each $P < .001$). Group-by-regimen interactions were highly significant for all 3 of ACTH, cortisol, and Epi (each $P < .001$). In all cases, COPD was associated with lower responses to exercise over time. The covariate (no exercise effect) was a significant predictor for the same 3 hormones (each $P < .001$).

Time-averaged (40 minutes) mean hormone concentrations were examined first by two-way ANCOVA. Group (healthy vs COPD) significantly determined mean ACTH concentrations (lower in COPD) during exercise ($P = .044$) (Fig. 2A). Exercise intensity (none, submaximal, maximal) determined mean Epi and NE levels (both $P \leq .001$). There were significant interactions between group and exercise level for mean cortisol ($P = .022$) and NE ($P = .007$) concentrations. Post hoc multiple-comparison testing of time-averaged cortisol responses disclosed no further contrasts. Interactions between cohort and exercise level were due to (*a*) failure of COPD (but not healthy) subjects to elevate mean NE concentrations during maximal compared with no exercise ($P = .11$ COPD vs $P < .001$ healthy) and (*b*) lower mean NE values in COPD than healthy participants at maximal ($P = .010$) but not submaximal ($P = .998$) exercise.

Peak ACTH concentrations were influenced by both group ($P = .036$) and exercise gradation ($P = .026$) (Fig. 2B). In particular, peak ACTH values in COPD patients were lower. Group did not determine peak levels of the other 3 hormones ($.10 < P < .90$). However, there were significant main effects of exercise level on cortisol ($P = .040$), Epi ($P < .001$), and NE ($P < .001$). By post hoc analysis, maximal (compared with no) exercise increased peak concentrations of each hormone, namely, ACTH ($P = .034$), cortisol ($P = .037$), Epi ($P < .001$), and NE ($P < .001$), in the combined groups. Submaximal exercise stimulated peak NE release ($P = .003$ vs rest) with a similar

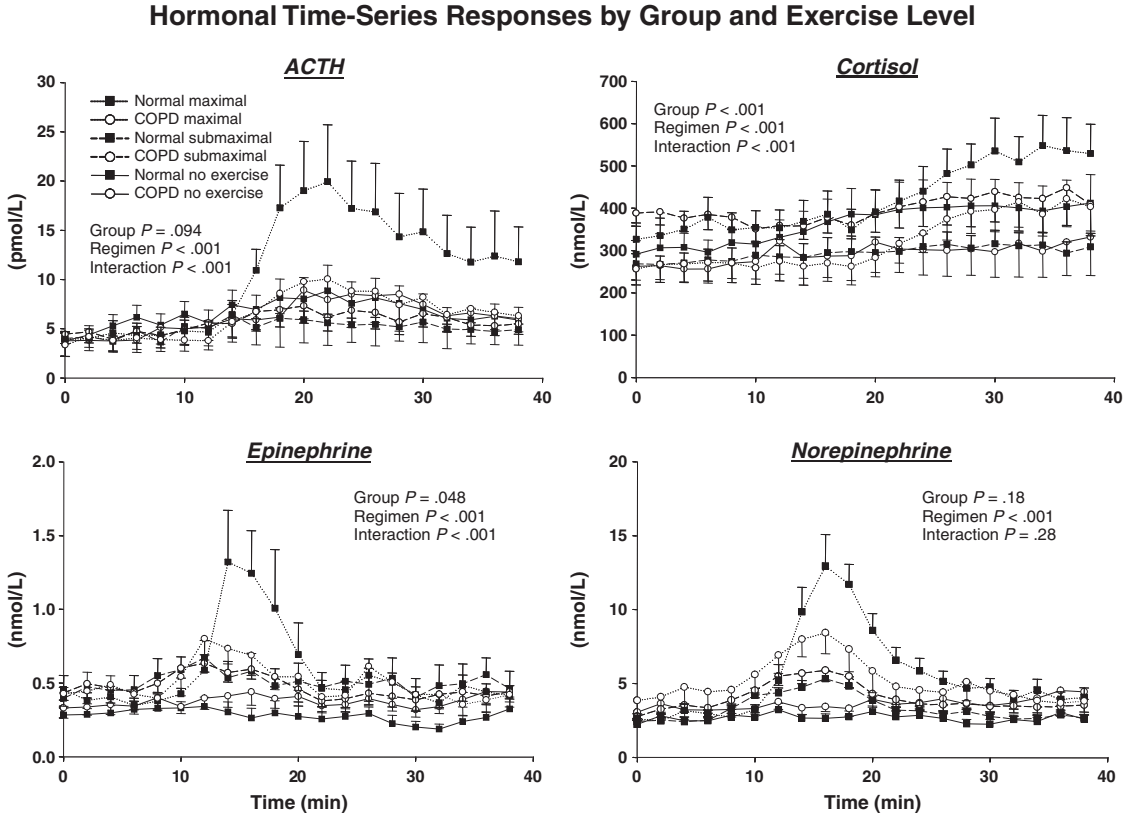
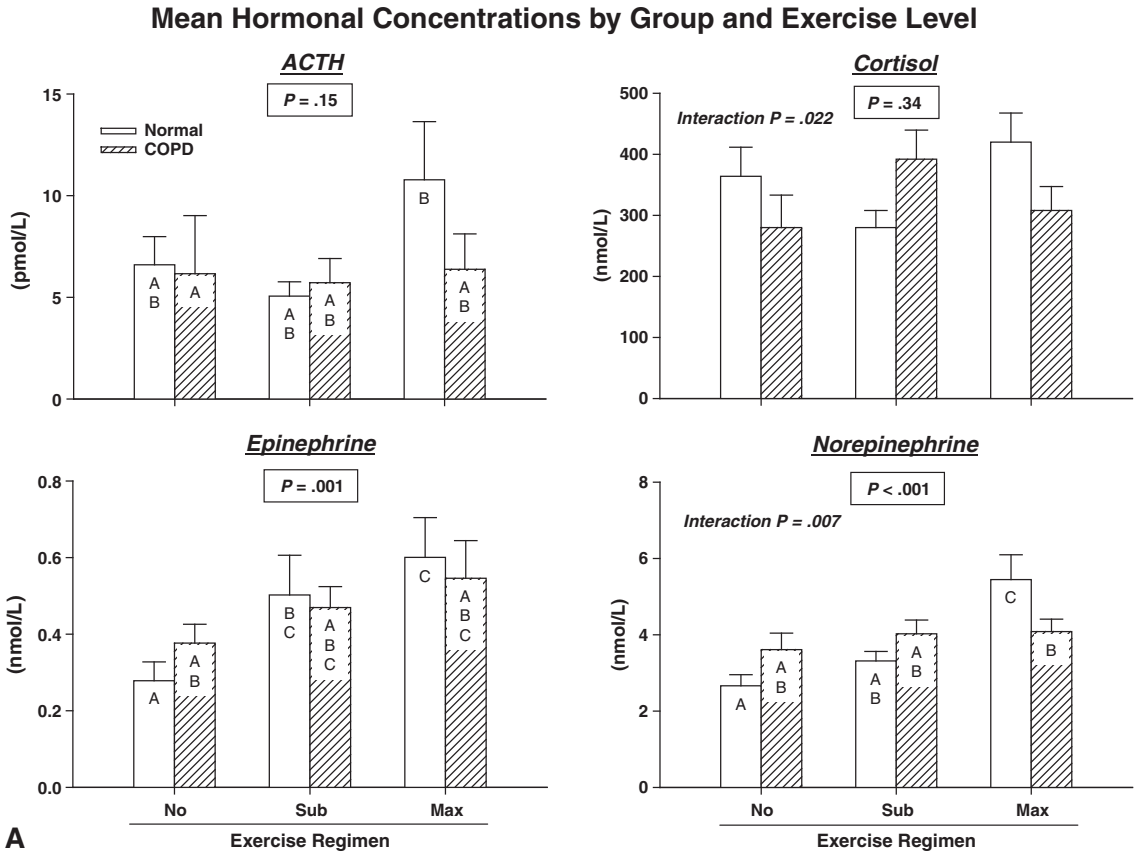
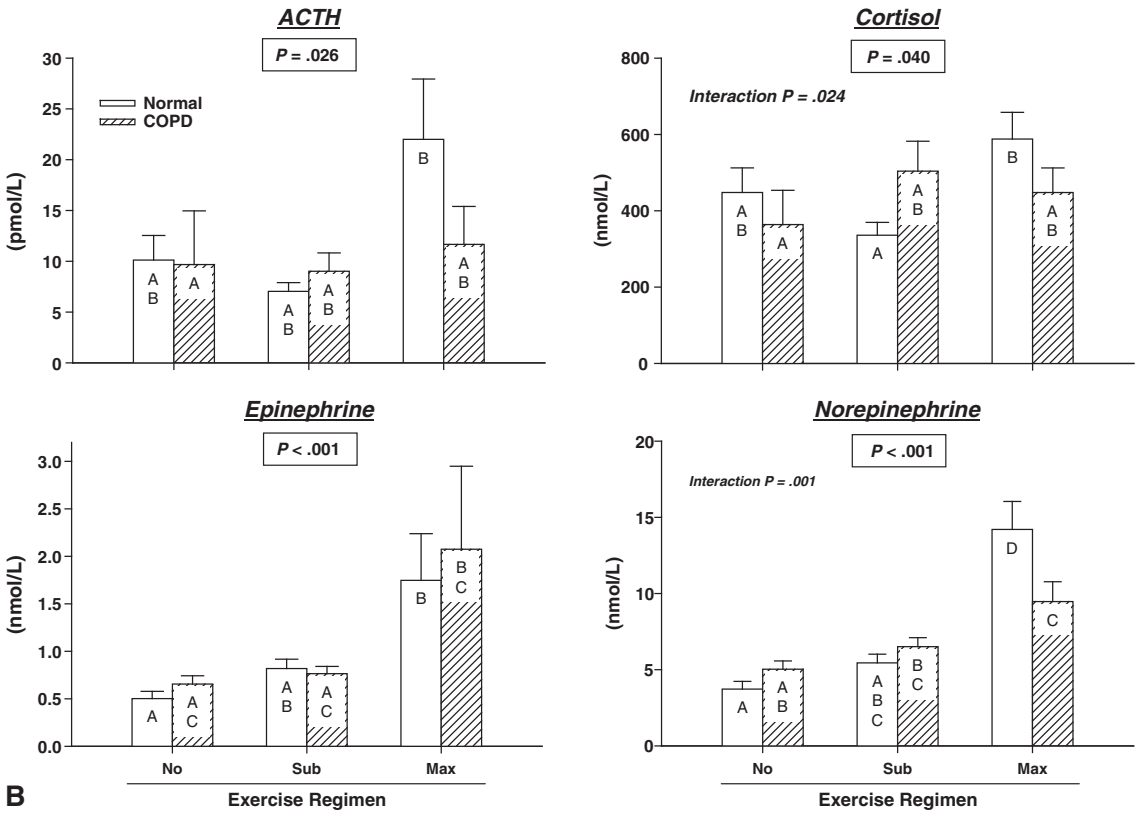



**Fig. 1 – Mean (±SEM) time-concentration profiles in healthy untrained men (n = 8) and patients with COPD (n = 9) studied at rest (baseline) and during submaximal (35% ± 5% of $Vo_{2max}$) or maximal exercise. Blood was sampled at 2-minute intervals for 40 minutes for measurements of ACTH (top left), cortisol (top right), Epi (bottom left), and NE (bottom right).**


Mean Hormonal Concentrations by Group and Exercise Level
ACTH
P = .15
Normal
COPD
(pmol/L)
Cortisol
P = .34
Interaction P = .022
(nmol/L)
Epinephrine
P = .001
(nmol/L)
Norepinephrine
P < .001
Interaction P = .007
(nmol/L)
No
Sub
Max
Exercise Regimen
A


Peak Hormonal Concentrations by Group and Exercise Level
ACTH
P = .026
Normal
COPD
(pmol/L)
Cortisol
P = .040
Interaction P = .024
(nmol/L)
Epinephrine
P < .001
(nmol/L)
Norepinephrine
P < .001
Interaction P = .001
(nmol/L)
No
Sub
Max
Exercise Regimen
B

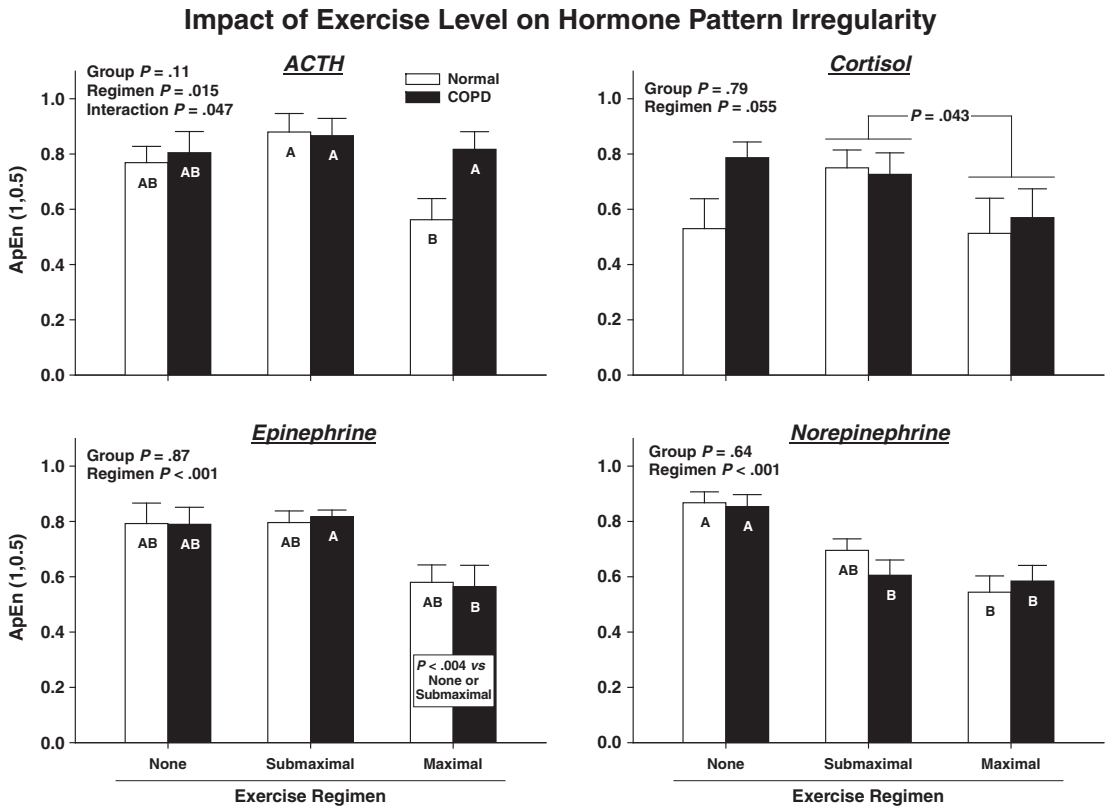



**Fig. 3 – Approximate entropy estimates of ACTH, cortisol, Epi, and NE secretory irregularity, a quantifiable measure of altered feedback/feedforward strength. Higher ApEn defines greater irregularity (greater process randomness). Data are presented otherwise as defined in Fig. 2.**

trend for peak Epi ($P = .070$). Maximal exceeded submaximal exercise effects for peak NE ($P < .001$) and Epi ($P = .005$) with an analogous trend-level effect for ACTH ($P = .075$). All covariate effects were $P \leq .001$. There were significant group-by-exercise interactions for peak cortisol ($P = .024$) and peak NE ($P = .001$) concentrations. In particular, only healthy participants had greater peak cortisol ($P = .048$) and NE ($P < .001$) concentrations after maximal than submaximal exercise. By the Tukey post hoc multiple-comparison test, healthy subjects attained higher peak NE concentrations during maximal exercise than COPD patients ($P = .001$).

The mechanisms underlying exercise's stimulation of peak hormone concentrations were assessed next by deconvolution analysis. Exercise intensity strongly and positively influenced pulsatile ACTH secretion ($P = .007$), pulsatile NE secretion ($P < .001$), and the mass of NE released per pulse ($P < .001$). Estimated half-lives of NE and Epi did not differ by group or exercise level (medians, 2.6 and 2.8 minutes, respectively). An unexpected mechanistic insight was abbreviation of cortisol secretory bursts (decreased mode) by maximal exercise in both groups ($P = .025$). In particular, cortisol secretory-burst mode averaged 3.2 ± 0.51 minutes during maximal and 6.4 ± 0.94 minutes during submaximal exercise.

Approximate entropy was used as a measure of physiological irregularity. Fig. 3 shows that there were no group effects on ApEn. Exercise intensity was associated with reduced ApEn for each of ACTH ($P = .015$), cortisol ($P = .055$), Epi ($P < .001$), and NE ($P < .001$). The ApEn values of ACTH ($P = .011$), cortisol ($P = .043$), and Epi ($P = .001$) were lower during maximal than submaximal exercise. Decreased ApEn would denote decreased pattern irregularity (increased relative orderliness). In addition, exercise interacted with group to determine ACTH irregularity ($P = .047$ for interaction). Specifically, ACTH irregularity decreased less in COPD than healthy subjects with maximal exercise (Tukey test $P = .042$).

Cross-ApEn provides an objective measure of joint asynchrony, wherein higher values denote more asynchrony (less pairwise synchrony). Adrenocorticotropic hormone–cortisol feedforward cross-ApEn fell (synchrony increased) during maximal compared with submaximal exercise in healthy

**Fig. 2 – Mean (A) and peak (B) plasma concentrations of ACTH, cortisol, Epi, and NE assessed by 2-way ANCOVA. Means with unshared (unique) alphabetic superscripts (such as A vs C, but not A vs AB) are significantly different by the Tukey honestly significantly different multiple-comparison test ($P < .05$). Open and hatched bars denote control and COPD subjects, respectively.**

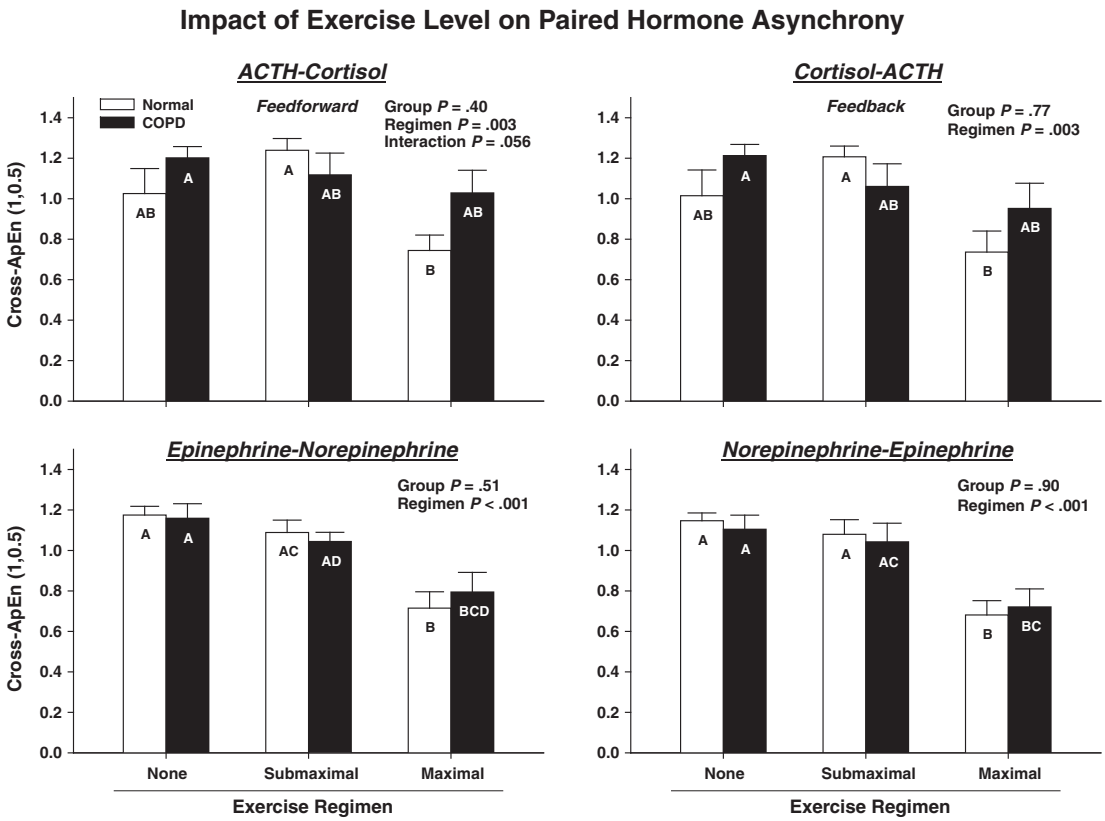



**Fig. 4 – Cross-ApEn estimates of joint (pairwise) asynchrony between ACTH and cortisol (feedforward) and between cortisol and ACTH (feedback) and analogously for NE-ACTH and ACTH-NE. Higher cross-ApEn quantifies greater synchrony (less pattern coordination). See data presentation format in Fig. 2.**

subjects only ($P$ = .003 exercise effect, $P$ = .056 interaction) (Fig. 4). Cortisol-ACTH feedback cross-ApEn declined with exercise intensity ($P$ = .003), but without any interaction between intensity and group ($P$ = .108). Epinephrine-NE and NE-Epi cross-ApEn also decreased at $P$ < .001 with maximal exercise. Other hormone pairs (ACTH-Epi, ACTH-NE, Epi-ACTH, NE-ACTH) exhibited similar lowering of cross-ApEn during maximal exercise ($P$ < .005, except for Epi-ACTH cross-ApEn where $P$ = .021).

## 4. Discussion

Baseline (resting) ACTH, cortisol, and catecholamine concentrations sampled over 40 minutes were similar in healthy subjects and patients with COPD. However, exercise evoked significant group distinctions. Peak ACTH, cortisol, and Epi concentrations failed to rise in COPD patients; and peak NE concentrations increased less than in healthy subjects. Impaired ACTH and NE responses were due to selective attenuation of pulsatile hormone secretion and failure to regularize (as quantified by ApEn) ACTH secretion patterns. The abnormal responses in COPD could not be attributed to lower fitness per se because percentage $Vo_{2max}$ values were comparable in the 2 study cohorts and similar to those in other studies [9]. Diminished endocrine responses were also not due to reduced dyspneic stress because COPD patients at any given gradation of exercise reported more severe dyspnea (perceived exertion) as expected [23].

Borg-dyspnea scores increased rapidly after about 6 minutes of exercise at 36% ± 6% (COPD patients) and 23% ± 5% (controls) $Vo_{2max}$, akin to other studies [24]. It would seem that COPD patients report less subjective dyspnea acutely in their chronic dyspneic state. Based upon 2-minute sampling, the timing of peak hormone responses was later, namely, Epi, 14 minutes; NE, 16 minutes; ACTH, 22 minutes; and cortisol, 34 minutes. This sequence is consistent with evidence that central adrenergic outflow triggers corticotropic-axis activation [25]. Reduced responsiveness could suggest that this pathway is impaired in patients with COPD. Catecholamine drive of ACTH is central because peripheral infusions of Epi or NE do not elicit ACTH or cortisol secretion [26]. Greater hypoxia in COPD would not explain impaired sympathoadrenal responses because severe hypoxia stimulates rather than inhibits NE, Epi, ACTH, and cortisol secretion [5,10]. A possibility is that COPD patients release less corticotropin-releasing hormone (CRH), which would drive less ACTH secretion [27,28], and/or produce more somatostatin and natriuretic peptide [29,30], which would inhibit CRH-driven ACTH secretion more significantly [11,31,32]. Because exercise can induce ACTH secretion even during constant CRH infusion [33], other agonists like arginine vasopressin may be important as well [27].

Another finding was that maximal exercise enforces more regular patterns (lower ApEn) of ACTH, cortisol, NE, and Epi

release. This was true in both study groups, except for ACTH regularization, which failed to occur in COPD patients. Based upon empirical and theoretic considerations, regularization of ACTH secretion requires muting of glucocorticoid feedback [19,34,35]. Thus, COPD patients might be unable to disinhibit cortisol's feedback onto ACTH during exercise. Withdrawal not only of glucocorticoid but also of GABAergic inhibition may be required for ACTH release during exercise [36]. Whatever the proximate mechanisms, corticotropic and adrenergic responses are proportional to relative workload (power output), expressible as percentage $Vo_{2max}$ [10,37-39]. The latter was similar in healthy volunteers and COPD patients, indicating that other mechanisms are responsible for decreased corticotropic responses in COPD. A possibility is that the mechanisms are similar to those in chronic fatigue syndrome [40].

Caveats include the possibility of carryover or training-like effects of the 3 exercise sessions. However, all studies were scheduled at least 72 hours apart; and the same order of study was applied to both groups. Moreover, an additional rest session separated the active-exercise bouts. Although BMI strongly inhibits the effect of exercise on GH secretion, its effects on exercise-stimulated ACTH and cortisol secretion are less well delineated. Whereas many factors might influence exercise effects, precautionary exclusions were concomitant use of mineralocorticoid-receptor antagonists (such as spironolactone) or calcium-channel antagonists (such as diltiazem) [41,42], and weight loss or the use of glucocorticoids within 3 months. Angiotensin-converting enzyme inhibitors were also disallowed [38]. Although all COPD subjects denied recent smoking, acute nicotine exposure would be expected to potentiate rather than attenuate ACTH and cortisol release [43]. The statistical similarity of ages would not necessarily exclude a less evident influence of a small age difference on the hormonal data. The study was not powered to answer this question.

In conclusion, men with stable COPD fail to achieve normal exercise-induced corticotropic axis and adrenomedullary outflow. The basis for joint defects in the amplitude and the regularity of stress-hormone release will require further study.

## Acknowledgment

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