

Respiratory and Skeletal Muscles in Hypogonadal Men with Chronic Obstructive Pulmonary Disease

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Hypogonadism, found in about one-third of patients with chronic obstructive pulmonary disease (COPD), has potential for decreasing muscle mass and muscle performance. Compared with eugonadal patients, we hypothesized that hypogonadal patients with COPD have decreased respiratory and skeletal muscle performance. Nineteen hypogonadal and 20 eugonadal men with COPD (FEV_1 1.14 ± 0.08 and 1.17 ± 0.11 L [standard error], respectively) were studied. Diaphragmatic contractility, assessed as transdiaphragmatic twitch pressure generated by phrenic nerve stimulation, was similar in hypogonadal and eugonadal patients: 20.6 ± 2.2 and 19.8 ± 2.5 cm H_2O , respectively. During progressive inspiratory threshold loading, hypogonadal and eugonadal patients had similar respiratory muscle endurance times (302 ± 29 and 313 ± 48 seconds, respectively) and airway pressure sustained during the last minute of loading (38.2 ± 3.0 and 40.5 ± 4.7 cm H_2O , respectively) (similar to predicted values in healthy subjects). Hypogonadal and eugonadal patients had equivalent limb muscle strength and endurance. During cycle exercise to exhaustion, exercise performance, gas exchange, and respiratory muscle recruitment (estimated by esophageal and gastric pressure swings during tidal breathing) were similar in both groups. In conclusion, hypogonadism does not decrease respiratory or limb muscle performance and exercise capacity in men with moderate-to-severe COPD who, for the most part, are not underweight.

Keywords: androgens; exercise tolerance; muscle fatigue; phrenic nerve; respiratory muscles

Peripheral muscle dysfunction, a common systemic complication in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) (1), commonly results from muscle wasting (2). The dysfunction is associated with muscle weakness (3), decreased exercise capacity (3, 4), impaired quality of life (5), and decreased survival (6), all of which occur independently of the impairment in lung function (7). The mechanisms leading to this form of muscle dysfunction are uncertain (8).

Several observations suggest that hypogonadism may contribute to the muscle dysfunction seen in men with COPD. First, hypogonadism has a high prevalence among these patients (7, 9, 10). Second, hypogonadism can cause decreases in nitrogen retention, lean body mass, and body weight (11, 12). Third, proinflammatory cytokines, which are increased in some patients with COPD with muscle wasting (13), can lead to decreased testosterone production (14, 15). Fourth, testosterone deficiency

can contribute to elevated levels of interleukin-6 (16), an inflammatory, pro-catabolic cytokine (17). Finally, administration of testosterone can increase myofibrillar protein synthesis (18, 19) and decrease protein breakdown (20).

Based on the above considerations, it is reasonable to surmise that hypogonadism might lead to impaired skeletal muscle function in patients with COPD, just as it does in hypogonadal subjects without COPD. Accordingly, we hypothesized that hypogonadism decreases respiratory and skeletal muscle performance in patients with COPD. To test this hypothesis, we compared muscle function in hypogonadal and eugonadal patients with moderate-to-severe COPD (21). The study is the first systematic assessment of the contractile response of the diaphragm to phrenic nerve stimulation (a technique that circumvents the problems of patient cooperation and motivation) and of respiratory muscle pressure output during respiratory loading, and of limb muscle performance and cycle exercise in hypogonadal and eugonadal men with COPD. Some of the results of these studies have been previously reported in abstract form (22, 23).

METHODS

Patients

Thirty-nine men with moderate-to-severe COPD were studied (Table 1). Nineteen patients were hypogonadal (free testosterone < 50 pg/ml) and 20 patients, matched for disease severity, were not (free testosterone ≥ 50 pg/ml). The hypogonadal threshold of 50 pg/ml was identified by assessing free testosterone concentrations in 139 healthy men. Appropriate institutional review boards approved the study and written consent was obtained.

Experimental Setup

Flow and pressure measurements. Flow and airway, esophageal (Pes), gastric (Pga), and transdiaphragmatic (Pdi) pressures were measured (24).

Compound diaphragmatic action potentials. These were recorded bilaterally using surface electrodes. Single bilateral phrenic nerve stimulation was performed using magnetic stimulators (24).

Experiment 1 (Respiratory Muscle Performance)

Eleven hypogonadal and 10 eugonadal patients participated in Experiment 1. After a resting period of 20 minutes, 5–10 nonpotentiated transdiaphragmatic twitches (twitch Pdi) were elicited at end exhalation. After the last stimulation, maximal transdiaphragmatic pressure (Pdimax) was measured as the best of 8–12 maximum inspiratory efforts. After each Pdimax, two stimulations were delivered to record potentiated twitch Pdi (a transient increase in twitch Pdi amplitude when nerve stimulation is preceded by a forceful contraction) (25). Thereafter, respiratory muscle endurance was tested with a progressive inspiratory threshold loading protocol (26) (see online supplement). Loading was terminated when the patient was unable to sustain the breathing task despite strong encouragement.

At baseline and each minute during loading, patients were asked to indicate the level of dyspnea and inspiratory effort (Borg-scale) (27). Twenty minutes after loading, nonpotentiated twitch Pdi, potentiated twitch Pdi, and maximum inspiratory efforts were again recorded.

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TABLE 1. CHARACTERISTICS OF 19 HYPOGONADAL AND 20 EUGONADAL MEN WITH STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	Hypogonadal	Eugonadal	p Value
Age, yr	70 ± 2	67 ± 1	0.33
Free testosterone, pg/ml	27.1 ± 2.8	77.5 ± 5.0	0.0001
Total testosterone, ng/dl	174.4 ± 22.4	509 ± 41.9	0.0001
Luteinizing hormone, mIU/ml	7.2 ± 1.2	4.3 ± 0.4	0.03
Body mass index, kg/m ²	28.4 ± 2.0	26.2 ± 1.0	0.31
FEV ₁ , L	1.14 ± 0.08	1.17 ± 0.11	0.83
FEV ₁ , percent predicted	38.6 ± 2.9	37.5 ± 3.1	0.80
FEV ₁ /FVC, %	44.4 ± 2.4	41.3 ± 3.2	0.44
FRC, L	5.2 ± 0.3	5.5 ± 0.4	0.55
TLc, L	7.3 ± 0.3	7.6 ± 0.4	0.54
pH	7.41 ± 0.01	7.42 ± 0.01	0.36
Pa _{CO₂} , mm Hg	41.9 ± 1.0	42.0 ± 1.4	0.60
Pa _{O₂} , mm Hg	69.4 ± 2.2	69.2 ± 2.5	0.96

Data are means ± SE.

To determine whether differences in Pdimax between the two groups were caused by differences in voluntary activation of the diaphragm, the intensity of central drive was quantified with the twitch-interpolation technique (24) before and 20 minutes after loading.

Experiment 2 (Limb Muscle Strength and Endurance)

Strength and endurance of handgrip were tested in 9 hypogonadal and 10 eugonadal patients (28). Strength and endurance of quadriceps (knee extension) were tested in 10 hypogonadal and 10 eugonadal patients (28) (see online supplement).

Experiment 3 (Exercise Capacity)

Ten hypogonadal and 10 eugonadal patients participated in Experiment 3. Maximum exercise capacity was measured using an incremental protocol (bicycle ergometer). Load was increased by 10-watt increments in power every 2 minutes until volitional exhaustion. Every 2 minutes during exercise patients were asked to indicate level breathlessness and leg effort (Borg-scale) (27). Respiratory muscle recruitment (estimated by Pes and Pga swings during tidal breathing) was continuously monitored.

Physiologic Measurements

Transdiaphragmatic twitch pressure. Criteria for acceptable twitch responses are listed in the online supplement. The within-occasion coefficient of variation for nonpotentiated twitch Pdi ranged from 1.6 to 10.3% (mean 5.8%). The within-occasion coefficient of variation for potentiated twitch Pdi ranged from 2.6 to 10.5% (mean 6.8%).

Respiratory mechanics and effort indices. Inspiratory resistance of the lung, dynamic compliance of the lung, and intrinsic positive end-expiratory pressure were computed according to standard formulae (29). Pressure time product of the inspiratory muscles (PTPes) and of the diaphragm (PTPdi) were calculated using standard formulae (29). The relative contribution of the different respiratory muscles to tidal breathing was assessed as the ratio of swings in Pga to swings in Pes ($\Delta Pga/\Delta Pes$) (29).

Data Analysis

Analysis of variance and Newman-Keuls test of multiple comparisons between individual means were used as needed. Further methodologic details are available in the online supplement.

RESULTS

With the exception of free and total testosterone concentrations, the two groups of patients were well matched for age and severity of COPD (Table 1). The two groups displayed equivalent pulmonary mechanics and minute ventilation ($\dot{V}E$) during resting

breathing (Table 2). Of the 19 hypogonadal patients, 14 had low or inappropriately normal luteinizing hormone concentration compatible with hypogonadotropic hypogonadism and 4 had elevated luteinizing hormone concentration compatible with testicular dysfunction (Table 1). In one patient, luteinizing hormone concentration was not measured. Three of the 19 hypogonadal patients and 1 of the 20 eugonadal patients were underweight (body mass index less < 21) (30). Patients in both groups were receiving long-term treatment with β agonists (n = 38), ipratropium bromide (n = 31), inhaled steroids (n = 26), and theophylline (n = 7). Six hypogonadal and two eugonadal patients were receiving prednisone (range: 2.5 mg every other day to 20 mg/day).

Experiment 1

Diaphragmatic contractility. The values of the nonpotentiated twitch Pdi and potentiated twitch Pdi at baseline were virtually identical in the two patient groups (Figure 1), and there was no correlation between free-testosterone concentrations and twitch pressures. The value of Pdimax at baseline was equivalent in the hypogonadal, 94.8 ± 12.0 cm H₂O, and eugonadal patients, 110.5 ± 15.3 cm H₂O (p = 0.43). When performing maximal inspiratory efforts, four hypogonadal and eight eugonadal patients had a rise in Pga of more than 25 cm H₂O. This degree of rise indicates that these patients recruited their expiratory muscles while performing the maximum voluntary diaphragmatic contraction (Mueller-expulsive maneuver) (31, 32). Free-testosterone concentrations did not correlate with Pdimax.

Endurance of the respiratory muscles. Endurance time was equivalent in the hypogonadal (302 ± 29 seconds) and eugonadal patients (313 ± 48 seconds), and there was no correlation between duration of loading and concentrations of free testosterone. The load sustained during threshold loading (Figure 2) and respiratory muscle pressure output (PTPes and PTPdi), and perceived ratings of air hunger and inspiratory effort were equivalent in the two groups (Figure 3). The lack of difference in ratings of perceived air hunger and inspiratory effort between the groups suggests that patients exerted themselves to the same extent (Figure 3).

Twenty minutes after the conclusion of endurance testing, nonpotentiated twitch Pdi and potentiated twitch Pdi—a more sensitive indicator of contractile fatigue than nonpotentiated twitch Pdi (27, 33)—were equivalent in the two groups and neither value was different from baseline (Figure 1). Pdimax (data not shown) showed the same pattern as did twitch pressures.

At baseline, twitch interpolation yielded a maximum voluntary activation index of the diaphragm of $85 \pm 5\%$ in the hypogonadal and $88 \pm 6\%$ in the eugonadal patients (p = 0.71). Twenty minutes later, the index was $88 \pm 3\%$ in the hypogonadal and $89 \pm 4\%$ in the eugonadal patients; neither value was different from baseline. In both hypogonadal and eugonadal patients, the mean Pdimax recorded during interpolation was approximately 10 cm H₂O lower than the corresponding value during maximal efforts performed without interpolation. That is, maximal efforts performed without interpolation activated the diaphragm slightly more than the extent measured by the voluntary activation index.

Experiment 2

The strength of the quadriceps (dominant leg) determined by maximal isometric knee extension (28) was 96.4 ± 5.5 lbs in the hypogonadal and 95.0 ± 4.7 lbs in the eugonadal patients (p = 0.85). Isometric endurance time measured as the time each patient could maintain a contraction at 50% of maximum with the dominant leg (28) was equivalent in the hypogonadal (75 ± 7 seconds) and eugonadal patients (63 ± 5 seconds, p = 0.16).

TABLE 2. VENTILATION AND PULMONARY MECHANICS DURING RESTING BREATHING IN THE HYPOGONADAL AND EUGONADAL MEN WITH STABLE COPD WHO PARTICIPATED IN EXPERIMENT 1

	Hypogonadal	Eugonadal	p Value
Respiratory frequency, breaths/min	17 ± 3	17 ± 2	0.95
Tidal volume, L	0.53 ± 0.06	0.59 ± 0.05	0.49
Intrinsic positive end-expiratory pressure, cm H ₂ O	2.2 ± 0.4	2.0 ± 0.5	0.69
Inspiratory resistance of the lung, cm H ₂ O/L/s	7.8 ± 0.4	7.9 ± 0.7	0.90
Dynamic compliance of the lung, ml/cm H ₂ O	251 ± 35	282 ± 37	0.54

Data are means ± SE.

Handgrip strength (dominant arm) was 94 ± 7 kPa in the hypogonadal and 95 ± 7 kPa in the eugonadal patients ($p = 0.90$). Handgrip endurance, measured as the time each patient could maintain a contraction at 50% of maximum with the dominant arm (28) was equivalent in the hypogonadal (71 ± 4 seconds) and eugonadal patients (76 ± 7 seconds, $p = 0.57$). Free-testosterone concentrations did not correlate with handgrip or quadriceps muscle strength or endurance.

Experiment 3

The responses to incremental exercise are shown in Figures 4 and 5. Exercise capacity was considerably less in both groups than in healthy subjects (maximum oxygen consumption was 39% of predicted in the hypogonadal and 37% of predicted in the eugonadal patients) (34). Absence of ventilatory reserve at peak exercise (\dot{V}_E to predicted maximal voluntary ventilation ratio of 1.1 ± 0.1 in the hypogonadal and 1.1 ± 0.1 in the eugonadal patients) indicates that patients reached maximum intensity.

Duration of exercise was equivalent in the hypogonadal (629 ± 79 seconds) and eugonadal patients (613 ± 94 seconds). Similarly, the two groups achieved equivalent maximum work rate during exercise (Figure 4, left upper panel). \dot{V}_E , O_2 consumption, CO_2 production, perceived breathlessness and perceived leg effort, and respiratory muscle pressure output and recruitment during exercise were equivalent in the two groups (Figures 4 and 5). Excessive dyspnea, with or without leg fatigue, was the most common reason for stopping exercising in the hypogonadal (80%) and eugonadal (90%) patients. The level of exercise-induced symptoms was equivalent to that reported by other investigators (35, 36). As with threshold loading, the lack of

difference in ratings of perceived dyspnea and leg effort between the two groups suggests that the patients exerted themselves to the same extent (Figure 4). As with tests of respiratory muscle strength and endurance and tests of limb muscle strength and endurance, free-testosterone concentrations did not correlate with maximum work rate.

DISCUSSION

This is the first report of systematic measurements of the contractile response of the diaphragm to phrenic nerve stimulation, respiratory-muscle pressure output during respiratory loading, and of limb muscle performance and cycle exercise in hypogonadal and eugonadal men with COPD. The major finding is that hypogonadism does not decrease respiratory muscle or limb muscle performance or decrease exercise capacity in men with COPD who, for the most part, are not underweight.

Respiratory Muscle Performance and Hypogonadism

Transdiaphragmatic pressure elicited by phrenic nerve stimulation was used as an objective and reproducible tool to quantify diaphragmatic contractility. Major determinants of transdiaphragmatic twitch pressure are contraction history (potentiation and fatigue) and lung volume (25, 27). By design, contraction history of the diaphragm was controlled and lung volumes were equivalent in the two patient groups (see Table E1 in the online supplement). Equivalence of transdiaphragmatic twitch pressures therefore signifies equal diaphragmatic contractility in the two groups.

The response to threshold loading in terms of duration, perceived inspiratory effort, perceived air hunger, sustained inspiratory

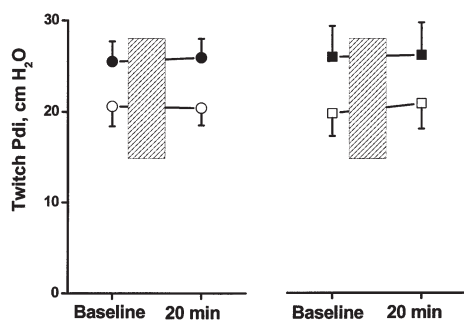


Figure 1. Potentiated (solid symbols) and nonpotentiated (open symbols) transdiaphragmatic twitch pressure (twitch Pdi) in 10 hypogonadal (left panel, circles) and 10 eugonadal (right panel, squares) men with COPD recorded before (baseline) and 20 minutes after conclusion of task-failure protocol. Potentiated and nonpotentiated twitch Pdi values were not affected by hormonal status or by threshold loading to task failure. Values are means ± SE.

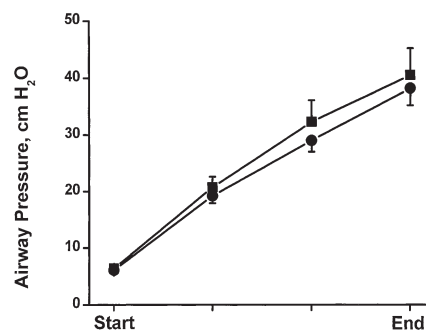


Figure 2. Airway pressure during inspiratory threshold loading in 11 hypogonadal (closed circles) and 9 eugonadal patients (closed squares) during inspiratory threshold loading. Between the start and end of inspiratory threshold loading increases in airway pressure occurred in both groups ($p < 0.0001$). Over the course of inspiratory threshold loading airway pressures were similar in both groups ($p = 0.53$). Bars represent SE (airway pressure data are based on nine eugonadal patients because the airway pressure transducer malfunctioned in one).

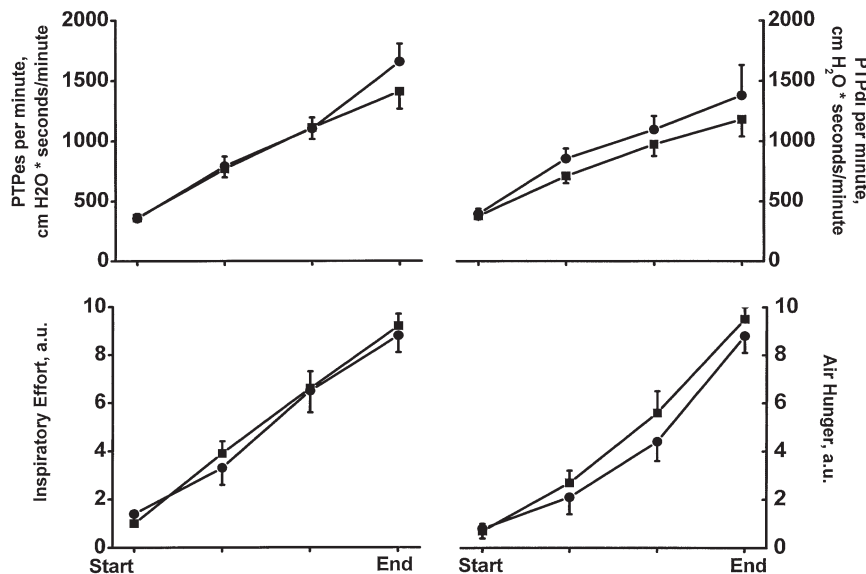


Figure 3. Esophageal pressure time product (PTPes) per minute (*upper left panel*), diaphragmatic pressure time product (PTPdi) per minute (*upper right panel*), and inspiratory effort (*bottom left panel*) and air hunger (*bottom right panel*), in hypogonadal (*closed circles*) and eugonadal patients (*closed squares*) during inspiratory threshold loading. Between the start and end of inspiratory threshold loading increases in all four variables occurred in both groups ($p < 0.0001$). Over the course of inspiratory threshold loading PTPes per minute (*upper left panel*), PTPdi per minute (*upper right panel*), and inspiratory effort and air hunger (*bottom panels*) were similar in both groups ($p > 0.36$ in all instances). Bars represent SE.

load, and respiratory muscle pressure output was equivalent in the two patient groups (Figures 2 and 3). Some (37, 38) but not all investigators (39–42) believe that learning can lead to improvement in subject performance during repeated threshold loading. During the last minute of loading, airway pressure in our hypogonadal (38.2 ± 3.0 cm H₂O) and eugonadal patients (40.5 ± 4.7 cm H₂O) was equivalent to that sustained by patients with COPD at a fourth

learning session (41 ± 6 cm H₂O) (37). Even if our patients could have achieved higher pressures through learning, all were equally naive, making the results robust.

If our patients had normal endurance, we predicted—using the equations of Johnson and collaborators (39)—that airway pressure at the end of loading would be 34.0 ± 2.9 cm H₂O in the hypogonadal and 39.0 ± 1.5 cm H₂O in the eugonadal patients.

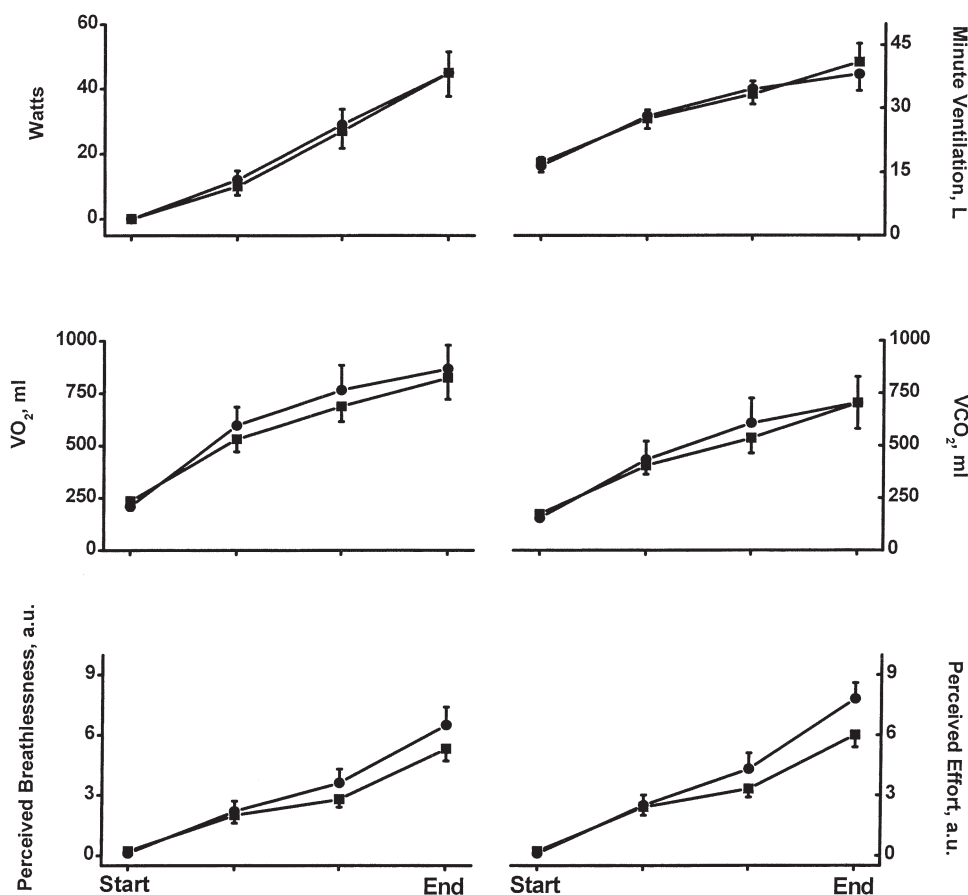


Figure 4. Workload (watts) (*upper left panel*), minute ventilation (*upper right panel*), oxygen consumption (V_{O_2}) (*middle left panel*), carbon dioxide production (V_{CO_2}) (*middle right panel*), and perceived breathlessness and perceived leg effort (*bottom panels*) in 10 hypogonadal (*closed circles*) and 10 eugonadal (*closed squares*) patients during whole body exercise. Between the start and end of whole body exercise, increases in all variables occurred in both groups ($p < 0.0001$). Over the course of whole body exercise, workload (*upper left panel*), minute ventilation (*upper right panel*), V_{O_2} (*middle left panel*), V_{CO_2} (*middle right panel*), and perceived breathlessness and perceived leg effort (*bottom panels*) were similar in both groups ($p > 0.20$ in all instances). Bars represent SE.

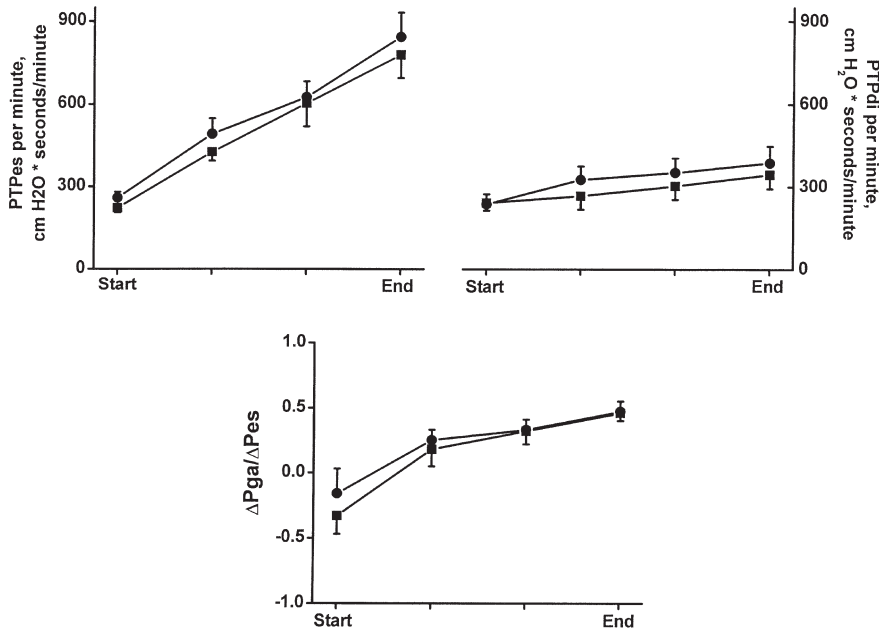


Figure 5. Esophageal pressure time product (PTPes) per minute (upper left panel), diaphragmatic pressure time product (PTPdi) per minute (upper right panel), and the ratio of swings in gastric pressure to swings in esophageal pressure swing ($\Delta P_{ga}/\Delta P_{es}$) (bottom panel)—an index of rib cage and expiratory muscle contribution to respiratory effort—in 9 hypogonadal (closed circles) and 10 eugonadal patients (closed squares) during whole body exercise. Between the start and end of whole body exercise all three variables increased in both groups ($p < 0.0001$ for PTPes and $\Delta P_{ga}/\Delta P_{es}$ in the hypogonadal and eugonadal patients, respectively, and $p = 0.0003$ and $p = 0.035$ for PTPdi in the hypogonadal and eugonadal patients, respectively). Over the course of whole body exercise, PTPes per minute, PTPdi per minute, and the ratio of swings in gastric pressure to swings in esophageal pressure were similar in both groups ($p > 0.47$ in all instances). Bars represent SE (data are based on nine eugonadal patients because one refused placement of esophageal and gastric balloons).

Those predictions are not different from the observed values: 38.2 ± 3.0 cm H₂O in hypogonadal and 40.5 ± 4.7 cm H₂O in eugonadal patients (Figure 2). All our patients, however, were hyperinflated (Table E1), a factor that can reduce endurance (43). Given the latter consideration, the observed normal endurance may represent a supranormal value in both groups. Increased endurance has also been noted by Newell and collaborators in 11 patients with COPD (44). Mechanisms that could increase endurance include increased adenosine triphosphate (ATP) generating capacity (relative to ATP utilization) in diaphragmatic muscle fibers (45) and transformation of fast (fatigue sensitive) to slow (fatigue resistant) fibers (46, 47).

Neither group of patients developed diaphragmatic fatigue after loading (Figure 1). The lack of diaphragmatic fatigue after loading is similar to its absence after failed weaning from mechanical ventilation in patients (29) and under more extreme conditions (loading to the point of respiratory arrest) in laboratory animals (48).

Why did hypogonadism not decrease respiratory strength and endurance? One, a conditioning effect of the increased inspiratory load (49) may have counterbalanced the catabolic effects of hypogonadism (11, 50). Two, most patients were not underweight. Three, respiratory muscles may be less sensitive to testosterone (and lack thereof) than the limb muscles: administration of massive doses of testosterone (20 mg/kg/day for 14 days) to rabbits did not produce increased diaphragmatic strength or endurance (48).

Limb Muscles and Exercise Performance

Strength and endurance of the limb muscles were equivalent in the two groups of patients. Likewise, the response to cycle exercise was equivalent in the two groups for all variables (Figures 4 and 5). Exercise capacity was decreased in both groups, and the decrease was not due to lack of motivation as indicated by the absence of ventilatory reserve at peak exercise (ratio of \dot{V}_E to predicted maximal voluntary ventilation of more than one). The equivalent exercise and limb muscle performance in the two groups is in line with the observation that testosterone has no effect on the endurance of leg muscles (20, 51) when administered at physiologic doses in otherwise healthy hypogonadal

men (20) or in healthy eugonadal men receiving a long-acting gonadotrophin-releasing hormone agonist (51). Likewise, the equivalent exercise and limb muscle performance in the two groups is also consistent with the observation that, in some studies, administration of physiologic doses of testosterone to hypogonadal men has no effect on the strength of leg muscles (52–54).

During exercise, hypogonadism had no effect on the pressure output of the inspiratory muscles (PTPes) and the diaphragm (PTPdi) and it had no effect on the pattern of respiratory muscle recruitment ($\Delta P_{ga}/\Delta P_{es}$) (Figure 5). Both groups exhibited a similar rise in the $\Delta P_{ga}/\Delta P_{es}$ ratio. The mechanism responsible for an increase in $\Delta P_{ga}/\Delta P_{es}$ is a rise in rib cage and the expiratory muscle contribution to tidal breathing as compared with the contribution of the diaphragm (29). Therefore, the similar increase in $\Delta P_{ga}/\Delta P_{es}$ ratios in both groups suggests that patients exhibited a progressively greater contribution of rib cage and expiratory muscles to tidal breathing.

The similar performance of the respiratory and peripheral muscles in the two groups is consistent with the observation that administration of anabolic steroids to unselected patients with COPD (55–57)—even if combined with pulmonary rehabilitation (55, 56) and inspiratory muscle training (56)—produces negligible (55) or no (56, 57) improvement in respiratory muscle function and no improvement in exercise endurance (55–57). The similar performance of the respiratory and peripheral muscles in the two groups is even more impressive considering that 32% of hypogonadal patients were on prednisone (2.5 mg every other day to 20 mg/day) and only 10% of eugonadal patients were on prednisone (10 mg/day, $p = 0.20$).

The fact that performance of the respiratory muscles and exercise capacity were similar in our hypogonadal and eugonadal men with COPD is consistent with the recent observations of Casaburi and collaborators (58). They found that neither inspiratory muscle strength nor whole body exercise capacity was altered by the administration of testosterone enanthate to patients with COPD who had variable serum testosterone levels. They (58), however, found that administration of testosterone produced a 17% increase in strength and endurance of the leg muscles, whereas we recorded no difference in peripheral muscle strength and endurance between our hypogonadal and eugonadal patients.

Whether the different leg performance between the two studies results from different inclusion criteria (i.e., some of the patients given testosterone in the study of Casaburi and collaborators (58) had normal testosterone levels) or from different techniques used to measure limb muscle performance (i.e., isometric vs. dynamic muscle testing) remains to be determined.

How can we reconcile the absence of observed effects (55–58) with the known anabolic actions of testosterone and anabolic steroids? One, muscle mass is maintained by several redundant pathways (7, 59), and, therefore, disturbances in one component are unlikely to be sufficient to cause dysfunction. Two, anabolic steroids may not further enhance the gains in respiratory muscle remodeling already achieved by the chronically increased load (45, 46, 58) or the endurance of the limb muscles achieved by exercise training—for some (55–57) but not all investigations (58). Indeed, physiologic or supraphysiologic doses of nandrolone have been shown to not further increase the gain in respiratory muscle performance above that achieved by training alone (59).

Clinical Implications

Indirect data suggest that androgen therapy might increase muscle function in hypogonadal patients with COPD. First, administration of testosterone in physiologic doses to androgen-deficient men increases lean body mass (20, 54) and muscle size (12, 20, 58, 60). Second, supraphysiologic doses of testosterone in healthy eugonadal men increase muscle mass and strength (61). Third, according to some (62) but not all investigators (59), administration of nandrolone to laboratory animals can increase the cross-sectional area of all types of diaphragmatic muscle fibers, the proportion of fatigue-resistant type IIa muscle fibers, and diaphragmatic strength (62)—but it can also have a deleterious effect on the muscle capillaries and mitochondria (63). Fourth, concomitant administration of androgens with corticosteroids can blunt the negative impact of corticosteroids on respiratory muscle function (48).

If patients are deficient in a hormone, it might seem self-evident to replenish normal levels. Long-term testosterone supplementation, however, can be associated with side effects, including increase in hematocrit, sleep apnea, prostatic hypertrophy, and those associated with alkylated androgens, cholestasis, peliosis hepatic, and hepatic failure (11, 50, 64). In a recent randomized trial, nandrolone was associated with an unexplained 9% incidence of respiratory failure and 6% mortality (65). Long-term effects of testosterone administration on the risk of prostate cancer and atherosclerotic heart disease remain unknown (50, 51). The value of testosterone treatment in older men with COPD (which includes most patients with COPD) remains to be demonstrated (66). In a just-published report from the Institute of Medicine, an expert committee concluded that unless more convincing studies are published, there is currently insufficient evidence to support testosterone therapy in older men (the case of most patients with COPD) (67).

Although our investigation was not designed to address whether testosterone replacement therapy may improve muscle performance in hypogonadal men with COPD, our results do not support such therapy if the sole goal is to improve respiratory or limb muscle function or increase exercise capacity. Our results leave open a provocative hypothesis that testosterone administration should be used in pharmacologic doses in either all patients with COPD (irrespective of the serum concentrations of the hormone) or in none of them. The onus for demonstrating the appropriateness of using testosterone supplementation in hypogonadal patients with COPD—with clinical characteristics similar to those reported in our investigation—remains on the physicians and investigators who advocate using testosterone “replacement” in patients.

Only 10% of our hypogonadal patients were underweight, therefore, we cannot exclude the possible benefit of administering androgens to hypogonadal patients with decreased muscle mass. The latter possibility, however, is tempered by the lack of clinically significant benefit of nandrolone on respiratory muscle function, exercise capacity, and health status over that achieved by rehabilitation alone in a group of 30 patients with COPD, most of whom (70%) had subnormal fat-free body mass (65).

In conclusion, hypogonadism does not decrease respiratory or limb muscle performance or decrease exercise capacity in men with moderate-to-severe COPD who, for the most part, are not underweight.

Conflict of Interest Statement: F.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; W.E.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; A.A.-T. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; A.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; C.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; M.J.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this article.

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