Journal of Allergy & Therapy
ISSN: 2155-6121

Budoff et al. J Aller Ther 2011, S2
DOI: 10.4172/2155-6121.S2-001

Research Article Open Access

Effect of Testosterone and Resistance Training on Cardiac Mass and Contractility in Men with COPD

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Abstract

Introduction: Testosterone therapy and resistance training have been demonstrated to improve muscle mass and strength in patients with testosterone deficiency. However the effects on cardiac mass and contractility of these interventions have not been identified in prospective placebo-controlled trials. The hypothesis of this trial was that resistance training and testosterone replacement would improve cardiac mass and contractility in male COPD patients with low testosterone levels.

Methods: We conducted a 10 week trial in a 2 by 2 factorial design, randomizing 53 patients to replacement doses of testosterone enanthate (100 mg weekly) or placebo, as well as to a program of lower extremity resistance training or no exercise. We performed rest and exercise cardiac computed tomography (CCT) studies before and after 10 weeks of therapy to evaluate right and left heart function. Patients were injected with 40-50 ml of non-ionic, iodinated contrast and cine CCT images were obtained at rest. Patients were exercised to 60% of their maximal work rate on a semi-supine ergometer, then re-injected with another bolus of 40-50 ml of contrast and re-imaged. We evaluated cardiac output and left ventricular (LV) and right ventricular (RV) mass, LV and RV stroke volume, ejection fractions and end-diastolic volumes at rest and exercise, before and after therapy.

Results: 42 men with COPD (mean FEV_1=40%pred. pre-bronchodilator) and low testosterone levels (mean=320ng/dl) completed the 10 week protocol. Factorial analysis demonstrated that testosterone, but not resistance training increased LV and RV mass (by 4.9% and 8.3%, respectively). Resistance training, but not testosterone, was associated with increased LV ejection fraction at rest and during exercise (by 5.5% and 4.4%, respectively). In the entire study group, increases in both left and right ventricular mass were correlated with increases in lean body mass (assessed by DEXA) (r=0.49 and r=0.65, respectively).

Conclusions: In men with COPD, testosterone replacement and strength training are associated with distinct alterations in cardiac structure and function. Specifically, resistance training improved ejection fraction, while testosterone increased lean body mass and LV mass.

Keywords: Cardiac computed tomography; Exercise; Testosterone; Chronic obstructive pulmonary disease

Introduction

Dysfunction of the muscles of ambulation contributes to exercise intolerance in chronic obstructive pulmonary disease (COPD). Men with COPD have been shown to have low testosterone levels which may further contribute to low muscle mass and muscle weakness. A few clinical studies of testosterone analogs in COPD have been published and have generally shown modest improvements in muscle mass, but have not shown unequivocal improvements in muscle strength [1-3]. Cellular studies have demonstrated androgen-mediated hypertropic responses to testosterone replacement [4], and myocardial hypertrophy associated with testosterone replacement has been quite reproducible in animals [5], our study is perhaps the first study to evaluate this effect in humans. More convincing studies are available to show that programs of resistance training increase muscle mass and strength in COPD [6].

The hypothesis of the present study was that resistance training and testosterone replacement would increase cardiac mass and function while improving muscle mass and strength of the muscles of ambulation in a cohort of men with COPD whose circulating testosterone level was low. We hypothesized that resistance training and/or testosterone supplementation would result in significant improvements in cardiac mass and/or ejection fraction assessed by cardiac CT.

Methods

Patient population: subjects

The study population consisted of 52 men who were in a stable phase of their COPD, without recent exacerbations. Women were excluded because testosterone supplementation at the dose utilized would likely yield virulization. Entry criteria included: age 55-80 years, forced expiratory volume in one second (FEV_1) ≤ 60% predicted [7] and an FEV1 to vital capacity (VC) ratio ≤ 60%. Subjects were ambulatory but not actively participating in an exercise program. Serum testosterone level was ≤ 400 ng/dl at screening, putting participants in the lower range of levels found in healthy elderly men. Patients unable to exercise, those with a creatinine elevated to twice the upper normal limits or with known contrast allergies were excluded. All patients gave written informed consent under a protocol approved by the Institutional Review Board. Patients were enrolled in a study to evaluate the effects of testosterone replacement, as well as resistance exercise training, on pulmonary, cardiac and muscle function. Hormonal, body composition

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Received July 04, 2011; **Accepted** September 17, 2011; **Published** September 20, 2011

Citation: Budoff MJ, Mao S, Rambod M, Oudiz RJ, Casaburi R (2011) Effect of Testosterone and Resistance Training on Cardiac Mass and Contractility in Men with COPD. J Aller Ther S2:001. doi:10.4172/2155-6121.S2-001

(by dual emission x-ray absorptometry (DEXA) scanning) and lower extremity muscle strength (by 1 repetition maximum (1RM) of leg press) responses to these interventions have been reported previously [8]. Lean body mass increase averaged 2.3kg with testosterone alone and 3.3kg with combined testosterone and resistance training ($p<0.001$). Leg press 1RM strength increase averaged 32kg with testosterone alone, 48 kg with strength training alone and 62kg with testosterone + strength training ($p<0.001$). We used these results to power the current study.

Study design

Subjects were randomized to one of the four following groups: 1) placebo injections and no resistance training, 2) testosterone injections and no resistance training, 3) placebo injections and resistance training or 4) testosterone injections and resistance training. To promote uniformity among these groups, randomization was stratified for age < or ≥ 67 years and FEV_1 < or ≥ 40% predicted. Investigators, study coordinators and subjects were blinded as to whether subjects received testosterone or placebo. As part of the parent protocol [9], patients underwent pulmonary function testing, body composition testing (by DEXA scan), leg muscle strength testing (by 1 repetition maximum) and incremental cycle ergometer testing to determine maximal exercise tolerance before and after the intervention. After screening, patients underwent a rest and exercise CT study, followed by a 10 week intervention period. The rest and exercise CT study was repeated within the week following the end of the intervention period.

Interventions

Resistance (Strength) training: The resistance training program focused on the muscles of ambulation. Sessions were held three times per week and were supervised by an experienced exercise trainer. Sessions were preceded by 5-10 minutes of warm-up and stretching exercises. Patients who were hypoxemic during exercise received supplemental oxygen by nasal cannula. Resistance training consisted of seated leg press, seated leg curl, seated leg extension, standing calf raise and seated ankle dorsiflexion exercises, providing overload of lower extremity major muscle groups. In each training session, subjects performed 3 sets of each of the 5 exercises. For the first 4 weeks, the training target was 3 sets of 12 repetitions at 60% of the pre-training one-repetition 45maximum. Training intensity was increased when subjects were able to complete all 36 repetitions for a given exercise. When 3 sets of 12 repetitions were again achieved, loads were again increased. After 4 weeks of training, one repetition maximum values were reassessed and used for the remaining 6 weeks. Subjects performed 4 sets of 8-10 repetitions, using 80% of the new one repetition maximum for each of the 5 training exercises; intensity was subsequently advanced as tolerated. All participants were asked to abstain from any additional resistance training or anything more than mild endurance exercise outside of the protocol.

Testosterone supplementation: Subjects received 100mg of testosterone enanthate in sesame oil (Delaestryl, 200mg/ml, BioTechnology General, East Brunswick, NJ) or placebo (sesame oil) by intramuscular injection weekly for 10 weeks.

Electron beam tomography studies

The CT studies were performed with an Imatron C-150XLP Ultrafast scanner (GE-Imatron, San Francisco, CA.). Patients underwent resting CT to assess left ventricular (LV) mass and right ventricular (RV) mass, as well as resting cardiac output and RV and LV ejection fractions and end-diastolic volumes. Tomographic images without contrast were obtained to identify the appropriate scan level. A continuous electrocardiogram monitor was attached to the patient to facilitate triggering of the CT. An 18 gauge intravenous catheter was placed in an antecubital vein. Patients were positioned supine on the scanner's couch then the couch was tilted axially 13 degrees with the feet down and slewed 13 degrees horizontally to the patient's right to facilitate left ventricular short axis views. The circulation time was obtained using a bolus injection of 10cc of non-ionic iodinated contrast medium, as previously described by Feiring [13]. Rest CT images were obtained by scanning sequential levels for one cardiac cycle at a rate of 17 scans per second using electrocardiographic triggering during an injection of 30-40 cc of non-ionic contrast material. Up to 20 images per cardiac cycle were obtained for each level of the ventricle. Twelve

Age, yr	67.4 ± 8.2
Height, cm	176 ± 8
Weight, kg	84.5 ± 18.9
FEV_1, % predicted	39.9 ± 12.3
FEV_1/VC (%)	41.7 ± 11.5
Testosterone, ng/dL	322 ± 148

Mean ± SD. FEV_1, forced expiratory volume in one second; VC, vital capacity

Table 1: Demographics, Pulmonary Function and Testosterone Level at Study Entry for 42 Men with COPD.

Variable	Pre-Intervention (Rest)	Pre-Intervention (Exercise)	
Heart Rate (bpm)	77.3 ± 14.6	108.3 ± 15.4	
LV Stroke Volume (ml)	61.0 ± 18.7	77.8 ± 19.9	<0.001
Cardiac Output (l/min)	4.68 ± 1.32	8.05 ± 2.17	<0.001
LV EF (%)	57.5 ± 9.7	62.9 ± 9.4	<0.001
LV EDV (ml)	106.2 ± 34.5	126.8 ± 34.3	<0.001
LV Myocardial Mass (g)	125.7 ± 32.2	-----	
RV SV (ml)	60.2 ± 12.3	81.3 ± 16.6	<0.001
RV EDV (ml)	146.8 ± 34.5	178.6 ± 38.1	<0.001
RV EF (%)	40.7 ± 5.2	45.1 ± 6.1	<0.001
RV Myocardial Mass (g)	68.8 ± 11.6	-----	

LV, left ventricle; RV, right ventricle; EF, ejection fraction; EDV, end diastolic volume

Table 2: Computed Tomography Results at Study Entry in 42 Men with COPD.

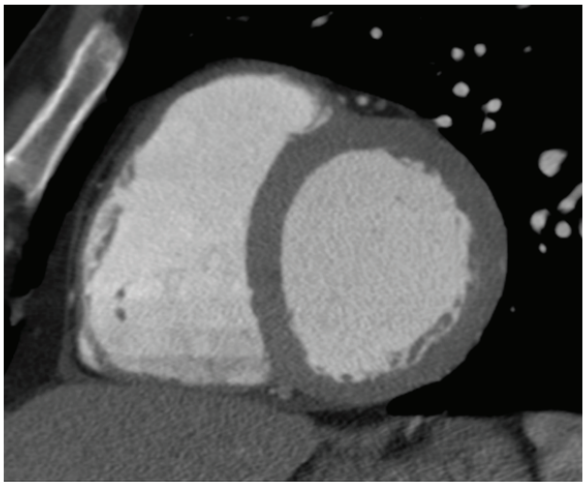

Figure 1: End diastolic image of the left ventricle. Contrast enhancement of the EBCT image allows clear distinction of the endocardial border. Utilizing the computerized program in the scanner, each level is divided into 12 equal segments and compared to the end systolic image at the same level. The program then calculates an ejection fraction for each segment.

levels, each with 8 millimeter slice thickness, were obtained during each contrast injection at a rate of 8-10 ml/second.

Exercise electron beam computed tomography: After the rest CT, patients underwent submaximal exercise using a stationary supine bicycle ergometer to assess for exercise-induced changes in cardiac output, LV and RV ejection fractions. The exercise protocol has been described previously [13,14]. Work rate was increased by 25 Watts every 2 minutes to 60% of the peak work rate determined during pre-intervention incremental cycle testing. A precordial electrocardiogram lead approximating V5 was monitored continuously throughout the test. Another circulation time was determined near peak exercise, and the patient's position was rechecked on the couch to ensure scanning at similar levels of the left ventricle as at rest. At 60% of peak work rate, the patients were re-injected with a similar bolus (30-40 cc) of non-ionic iodinated contrast material and rescanned to directly compare exercise results to the rest studies. The same protocol was used at post-

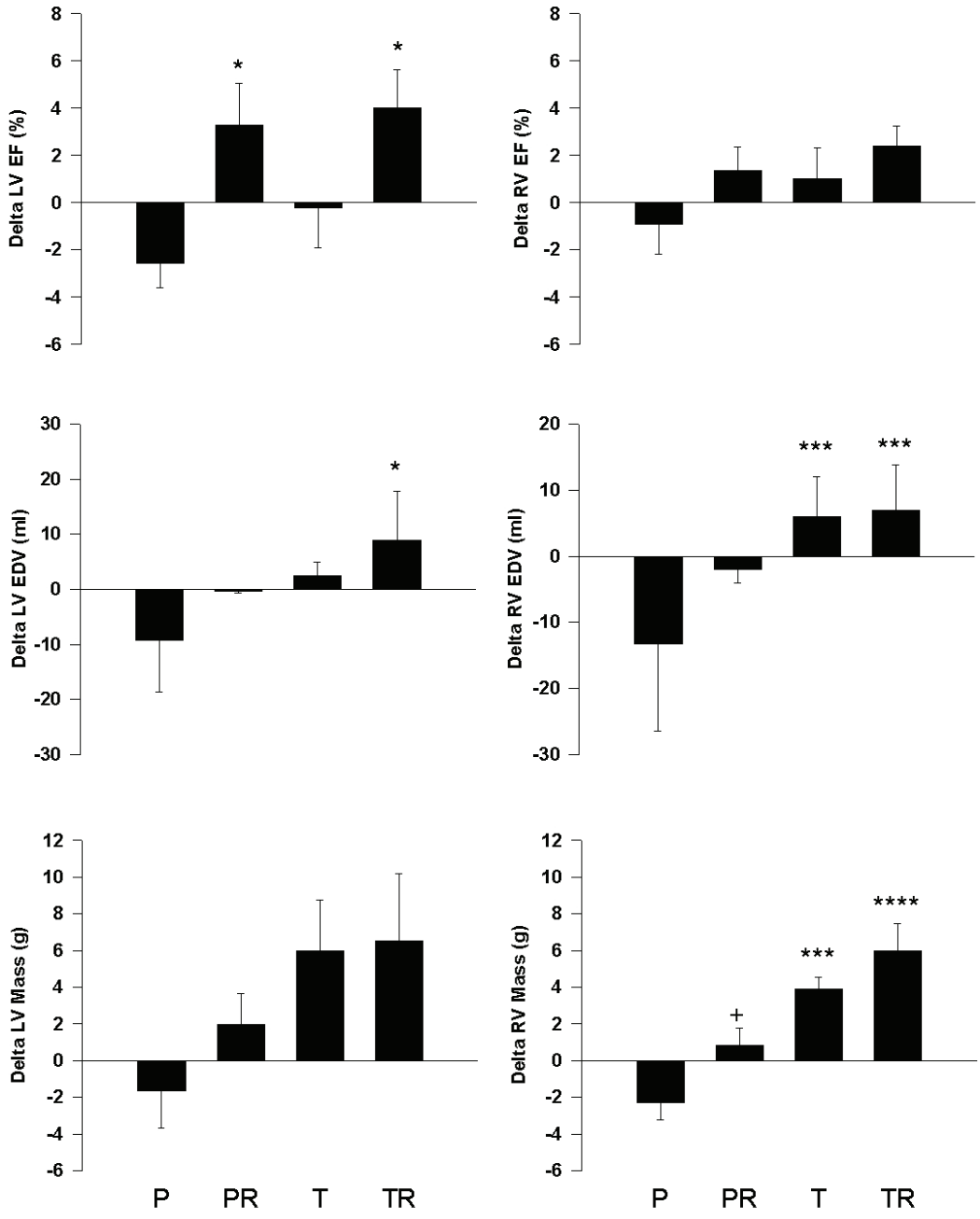

Figure 2: Changes induced by testosterone administration and/or resistance training in the four subject groups in cardiac variables at rest (bars represent mean and SE of change). P: placebo, no training; PR: placebo, resistance training; T: testosterone, no training; TR: testosterone, resistance training. Significant difference with respect to placebo-no training: *: p<0.05, ***: p<0.005, ****: p<0.001. Significant difference from testosterone-resistance training: +: p<0.05.

intervention (week 12) and patients were exercised at the same work rate in both pre- and post-intervention exercise CT tests.

Left and right ventricular ejection fraction assessment by CT: The CT images were evaluated by delineating the endocardium and epicardium at end-diastole and end-systole of each level of the heart by an investigator blinded to all demographics and treatment randomizations. The pre- and post-intervention measures were measured in random order, with the reader blinded to patient information and order of tests. On every 8 mm level (up to 12 per study), both right and left ventricular cavities were manually traced.

Each cross-sectional image of the left and right ventricle from base to apex was analyzed by a computerized wall motion analysis program [13]. Ejection fraction, end-systolic and end-diastolic volumes were calculated at each tomographic level. Using a computer summation program, global ejection fraction was obtained at rest and exercise as described previously [10,12,15]. Stroke volume was also calculated on every level, as well as the end-diastolic volume, end-systolic volume and myocardial mass. Total volumes and measures were a sum of all measures on every slice. Cardiac output was calculated from the total stroke volume times the heart rate. Myocardial mass was calculated for both the RV (not including the septum) and LV (including the septum and free wall).

Statistical analysis

All data are expressed as a mean ± standard deviation in text and tables and as ± standard error in figures. Differences among group baseline characteristics were determined using one-way analysis of variance (ANOVA). The changes between rest and exercise were analyzed using a paired t-test. Differences in responses to interventions among groups was determined with repeated measures ANOVA, using the Tukey post-hoc test to isolate differences between groups. Further, 2x2 factorial analysis, with testosterone administration and resistance training as the factors (with and without an interaction term), was utilized to determine whether these factors were significant predictors of changes in cardiac mass or contractility variables. Two-sided tests were used and significance was defined at the 0.05 level or below.

Results

Of the 52 patients randomized, 42 completed the protocol. Of the non-completers, one (in the testosterone + training group) was discontinued because of non-compliance with the protocol and 5 because of non-protocol related health problems (2 in the testosterone + training group and one each in the other 3 groups). Four additional patients did not undergo the follow up CT scan. Patients in the training groups completed at least 25 of the scheduled 30 sessions; those receiving testosterone averaged 27.5 sessions and those receiving placebo averaged 28.1 sessions. Patients tolerated the interventions well and no adverse events related to either training or to testosterone supplementation were recorded. Patient characteristics of the 42 subjects who completed the protocol are presented in Table 1; there were no significant differences among the four groups. On average, subjects had moderate to severe airflow obstruction on spirometry and

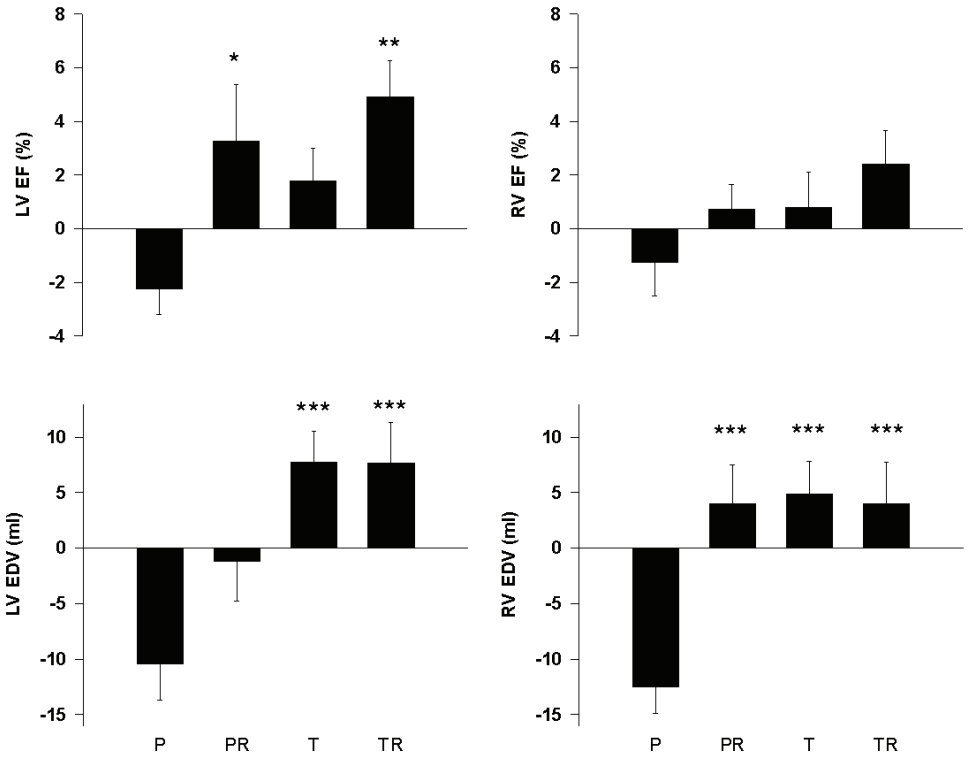

Figure 3: Changes induced by testosterone administration and/or resistance training in the four subject groups in cardiac variables during exercise (bars represent mean and SE of change). P: placebo, no training; PR: placebo, resistance training; T: testosterone, no training; TR: testosterone, resistance training. Significant difference with respect to placebo-no training: *: p<0.05, **: p<0.01; ***: p<0.005.

Variable	Regression Coefficient for Testosterone	P Value	Regression Coefficient for Resistance Training	P Value
LV Mass (g)	6.09	0.022	2.22	0.39
RV Mass (g)	5.68	<0.001	2.66	0.014
LV EF rest (%)	1.54	0.32	5.12	0.002
LV EF exercise (%)	2.82	0.065	4.44	0.005
RV EF rest (%)	1.47	0.2	1.88	0.1
RV EF exercise (%)	1.85	0.13	1.82	0.13

LV, left ventricle; RV, right ventricle; EF, ejection fraction.

Table 3: Regression coefficients for linear regression model to determine whether testosterone and/or resistance training were significant predictors of changes in cardiac mass or contractility variables. Primarily, LV and RV mass increased with testosterone, while ejection fractions increased with resistance training.

circulating testosterone levels averaged 322ng/dL, substantially less than the 500-1000 ng/dl range generally seen in healthy young men.

No patient had any complications during EBCT exercise testing or contrast infusion. EBCT variables at rest and during exercise at study entry for the 42 participants are presented in Table 2. There were no significant differences in any of these variables among the four groups. RV ejection fraction was lower than normal in the entire cohort. Exercise was associated with a 72% increase in cardiac output ($p<0.001$). With exercise, end-diastolic volume of both chambers increased but ejection fraction did not change appreciably.

Intervention-associated changes in ejection fraction and end-diastolic volumes: Figure 2 and Figure 3 present changes associated with the interventions in cardiac variables at rest and during exercise, respectively. As compared with the placebo-no training group, both groups performing resistance training increased LVEF both at rest (Figure 2) and during exercise (Figure 3) with differences averaging from 5 to 7 percentage points. Changes in RVEF did not achieve statistical significance. As compared with the placebo-no training group, LV end-diastolic volume increased at rest in the testosterone plus resistance training group and in during exercise in both groups that received testosterone. As compared with the placebo-no training group, RV end-diastolic volume increased at rest in both groups that received testosterone and during exercise in all three other groups.

Intervention-associated changes in myocardial mass: As compared with the placebo-no training group, increase in left ventricular mass just failed to achieve statistical significance ($p = 0.17$ and 0.12 in the testosterone and testosterone plus resistance training groups, respectively) and right ventricular mass increased significantly in the two groups that received testosterone. These increases averaged 6-8 g (or roughly 6% and 10%), respectively. No significant change in the mass of either ventricle was seen in the group that received placebo and resistance training.

Factorial analysis: To determine whether testosterone and resistance training exerted independent and significant effects on cardiac mass and contractility variables, data from all subjects were entered into a linear regression model of the form:

$$\Delta y = a_1 [\text{testosterone}] + a_2 [\text{resistance training}] + c$$

Where the independent variables assumed values of 1 or 0 depending on whether the individual received or did not receive the intervention and the independent variables are changes in measures of cardiac mass or contractility. The coefficients a_1 and a_2 are presented in Table 3. From this analysis, it is clear that receiving testosterone, but not resistance training, contributes significantly to increases in both right and left ventricular mass. Receiving resistance training, but not testosterone, contributes significantly to increases in left ventricular ejection fraction both at rest and during exercise. Neither intervention achieves a statistically significant effect on right ventricular ejection fraction. When an interaction term of the form a_3 [testosterone]*[resistance training] was included in the model, a_3 did not achieve statistical significance in any case, and ANOVA yielded similar neutral results.

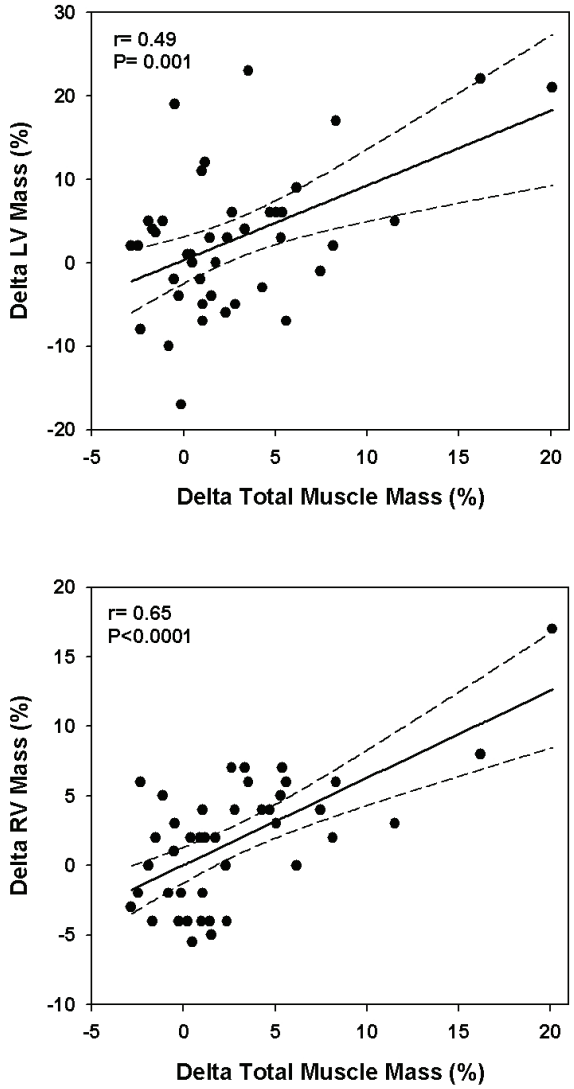

Figure 4: Correlation among subjects in change in right ventricular mass (Panel A) and left ventricular mass (Panel B) with whole body muscle mass, each expressed as a percent of the pre-intervention value. Solid line represents linear regression of data; dashed lines are 95% confidence limits of the regression.

Correlation analysis: Correlations among subjects of changes in cardiac mass and contractility with changes in body mass and leg muscle strength were determined. Changes in both left and right ventricular mass correlated with changes in whole body muscle mass (determined by DEXA scan) (r=0.49, p=0.001 and r=0.65, p<0.0001, respectively) (Figure 4). Changes in both rest and exercise left ventricular ejection fraction correlated with changes in leg muscle strength (assessed as 1 repetition maximum leg press) (r=0.369, p=0.016 and r=0.465, p=0.002, respectively).

Discussion

This is one of the first studies demonstrating that testosterone, but not resistance training, increased LV and RV mass (by 4.9% and 8.3%, respectively). Resistance training, but not testosterone, was associated with increased LV ejection fraction at rest and during exercise (by 5.5% and 4.4%, respectively). In the entire study group, increases in both left and right ventricular mass were correlated with increases in lean body mass (assessed by DEXA) (r=0.49 and r=0.65, respectively). Thus, in men with COPD, testosterone replacement and strength training are associated with distinct alterations in cardiac structure and function.

The cardiac effects of anabolic steroids have been demonstrated predominantly in body builders. Several studies demonstrated an increase in left ventricular end diastolic volume, left ventricular mass and/or worsening diastolic function [11-13], while other studies demonstrated no cardiovascular changes with anabolic steroid use [14-16]. However, in bodybuilding, the doses used are often 10-100 times the therapeutic dose; in one report involving 24 weight lifters, the lowest dose was 350% of the usual therapeutic dose [17]. Lower physiologic replacement doses of testosterone have demonstrated a beneficial effect on angina pectoris, exercise tolerance, exercise-induced ST segment depression and coronary diameter [18]. In a small randomized clinical trial of older men (n=209) with limitations in mobility and a high prevalence of chronic disease, the application of a testosterone gel was associated with increased muscle strength and an increased risk of cardiovascular adverse events [19]. Other data related to the potential cardiac safety or harm of testosterone comes from meta-analyses of small trials, epidemiologic studies or studies in bodybuilders taking high doses of androgenic steroids [20-22].

The ability to visualize both the right and left ventricles has proven difficult in prior studies using exercise radionuclide, echocardiographic and earlier CT imaging techniques [23-25]. Poor visualization of the right ventricle, a poorly defined endocardial surface, irregular right ventricular geometry, and limited reproducibility of exercise studies are important limitations of echocardiography in evaluating the left and right ventricle [26]. Cardiac exercise CT has been shown to have excellent sensitivity and specificity for detecting coronary disease and for assessing changes in both right and left ventricles [11-15,27,34]. CT also allows clear apical delineation, and breast shadows, obesity, the diaphragm or bowel do not cause attenuation, and excellent reproducibility has been demonstrated, with interstudy, intraobserver and interobserver variations were 0.01±1.4, 0.06±2.0 and 0.28±2.1% respectively [14,28,29,36].

In the present study, factorial analysis demonstrated that resistance training was associated with increases in LV ejection fraction (by 5.1% at rest and 4.4% with exercise, Table 3). This magnitude of change is clinically significant, on par with improvements seen with afterload therapy in congestive heart failure [30]. This is not surprising, as exercise has demonstrated improved outcomes in other cohorts of patients [31]. In contrast, the trend for RV ejection fraction to increase with resistance training did not achieve statistical significance.

Testosterone therapy was associated with increases in both LV and RV mass in this study (averaging 6.1g and 5.7g, respectively, Table 3). These increases correspond to approximately a 4.9% increase in LV and 8.3% increase in RV mass. The findings of increasing LV and RV mass in this study is consistent with animal data. A study of castrated rats demonstrated that testosterone replacement led to an increase in LV mass, returning it back to pre-castration levels [32]. The increase in LV mass was in proportion to the change in body weight: the left ventricular weight/body weight ratio did not change [37]. A similar increase in LV mass was seen in human long distance runners and weight lifters, with LV mass increasing only to the extent that lean body mass is increased [33].

Previous studies have demonstrated benefit of testosterone replacement to increase skeletal muscle mass [34]. In our cohort, replacement doses of testosterone yielded increase lean body mass. In the group as a whole, increases in both LV and RV mass were correlated with the changes in lean body mass (Figure 4), The implications for a COPD population are significant, as lean body mass is often reduced2 and improvements in both lean body mass and cardiac mass may lead to better long term outcomes [3]. Though cardiac and whole body muscle mass are measured by very different methods, these results suggest that cardiac and skeletal muscle mass are controlled by similar factors. Several studies have demonstrated that the dose response to testosterone is related to lean body mass and obesity [42], supporting this observation.

Limitations

Cardiac CT exercising testing requires semisupine positioning. While semisupine bicycle ergometry results in lower peak heart rates and less change in ejection fractions in some radionuclide studies, the ability to detect CAD was no different using upright or supine exercise in these studies [35-37]. Patients with contrast allergies, renal insufficiency and those unable to exercise cannot undergo this CT evaluation. Radiation doses with the protocols utilized in this study are low, and the total radiation doses that patients received for these combined protocols were <6 mSev [38]. Due to the limited number of patients in the study, it is possible that some of the trends in individual groups may not have reached statistical significance. It is also possible that the treatment duration was not long enough to see all cardiovascular effects of these two interventions.

Overall, there remains a paucity of randomized clinical trials evaluating the cardiovascular effects of testosterone replacement, especially on cardiac outcomes. Whether testosterone replacement represents an adaptive response to low testosterone levels (positive response of increasing strength of skeletal and/or cardiac muscle) or just universally increases myocardial mass regardless of baseline levels (potentially negative effect) needs to be demonstrated in prospective trials. Multiple different mechanisms have been proposed, and large prospective human trials are warranted to evaluate whether these cardiac effects have a positive or negative effect on long term outcomes in males with lower hormone levels. In this study, resistance training improved ejection fraction, while testosterone increased lean body mass and LV mass.

Acknowledgments

We thank Hamid Bakhsheshi, BSRT for his excellent technical assistance with this project. R. Casaburi occupies the Grancell/Burns Chair in the Rehabilitative Sciences.

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