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# Cardiac Structure and Function in Men with Prostate Cancer Receiving Androgen-Deprivation Therapy and the Effects of Recreational Small-Sided Football Training: A Randomized Controlled Trial

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## Abstract

**Purpose:** Androgen deprivation therapy (ADT) is a cornerstone in prostate cancer (PCa) management that prolongs PCa-free and overall survival, but effects of ADT on human cardiac function have not been investigated. We used echocardiography to examine cardiac structure and function in patients with prostate cancer receiving ADT and to determine whether an exercise intervention can elicit cardiac adaptations in these subjects. **Methods:** Forty-three patients with prostate cancer receiving ADT were randomized to 12 weeks football training (ST group; n = 20) or usual care (control [CO] group; n = 23). Cardiac function was assessed at baseline and after 12 weeks by comprehensive echocardiography. Peak oxygen consumption, blood pressure and peripheral microvascular function was also measured. **Results:** At baseline, no considerable echocardiographic abnormalities were observed. In the ST group, increases in left ventricular diastolic function variables including E/A ratio (P = 0.03), E' (P = 0.016), E'$_{TDIcolor}$ (P = 0.040) and in left atrial diameter

(P = 0.001) were observed after 12 weeks. In addition, diastolic blood pressure
(P = 0.027) and resting heart rate (P < 0.001) were reduced after ST. In the CO
group, no significant changes were observed in the examined variables after
12 weeks. Despite within group changes in the ST group, no significant differences were observed after 12 weeks between groups in echocardiographic
variables, peak oxygen consumption, blood pressure and peripheral microvascular function. **Conclusion:** In men with prostate cancer receiving ADT,
echocardiography showed no abnormalities in cardiac structure and function.
Twelve weeks of ST failed to elicit significant cardiovascular adaptations and
ADT may blunt cardiovascular adaptations to short-term exercise training.

## Keywords

## 1. Introduction

Androgen deprivation therapy (ADT) is a cornerstone in prostate cancer (PCa)
management that prolongs PCa-free and overall survival. However, ADT is associated with increased risk of cardiovascular disease (CVD) and risk factors
such as adiposity, type 2 diabetes, increased circulating lipid levels and augmented central aortic stiffness, along with reduction of muscle strength and
physical capacity [1]-[7]. Limited experimental evidence has also suggested that
ADT can influence cardiac function and in rats ADT is associated with left ventricular (LV) dysfunction, which can be ameliorated by exercise training (EX)
[8]. Exercise training level is inversely related to long term PCa survival and has
been documented as a feasible, safe and effective means for improvement of fitness, body composition and quality of life in PCa patients undergoing ADT [4]
[6] [9] [10] [11] [12]. Soccer training (ST) is akin to high intensity interval
training and while effects of ST have as yet not been examined in patients undergoing ADT, we have found that small-sided recreational ST elicits cardiovascular adaptations and marked improvements of physical capacity in, for
example, elderly healthy men, and men with hypertension or type 2 diabetes [13]
[14] [15] [16] [17]. Importantly, ST is associated with positive psychosocial interactions that augment social capital, improve quality of life and contain rational and action-oriented elements that have been requested by male cancer patients and is likely to improve long-term adherence to EX [18] [19].

In view of the increased risk of CVD in patients with PCa undergoing ADT, it
is important to determine if ADT is associated with cardiac abnormalities and
effects on cardiac adaptations to EX. We are, however, not aware of reports on
cardiac structure and function in patients with PCa undergoing ADT, and it is
unknown if EX can elicit similar cardiac adaptations in these patients as has
been observed in other subjects [4] [6] [9] [10] [11] [12] [14] [16] [20] [21] [22].
Comprehensive echocardiography with tissue Doppler imaging (TDI) and

speckle tracking analysis of 2D global systolic longitudinal strain (GLS) is a sensitive tool to detect subclinical cardiac dysfunction [23] [24] [25] [26]. Therefore, the purpose of the present study was to examine in men with PCa undergoing ADT: 1) cardiovascular structure and function by comprehensive echocardiography, and 2) cardiovascular adaptations in response to a short-term ST intervention.

## 2. Methods

### 2.1. Patients and Study Design

From March 2012 to December 2013, patients with histologically confirmed advanced or locally advanced PCa were recruited in Copenhagen Denmark. Study flow is presented in **Figure 1** and the full study design was recently reported [27]. Fifty-seven patients were found to be eligible for baseline testing and were randomized 1:1 to a 12 week structured EX program consisting of ST (ST group n = 29) or a usual care control group (CO; n = 28). Forty-three patients completed the study (ST group n = 20) and usual care control group (CO; n = 23). The study was approved by the Danish National Committee and all participants provided written informed consent. EX was performed as small-sided (4vs. 4; 5 vs. 5; or 6 vs. 6) recreational ST two-three times per week for 12 weeks. The patients in the CO group were encouraged to maintain their baseline physical activity level during the study. Clinicaltrials.gov identifier number NCT01711892.

### 2.2. Cardiovascular Function and Fitness

All subjects were examined at baseline and after 12 weeks by comprehensive transthoracic echocardiography as described previously [27]. Measurements of cardiac structure and function were obtained by standard 2D echocardiography and LVEF < 45% and peak early diastolic velocity E' < 9 cm/s was considered as
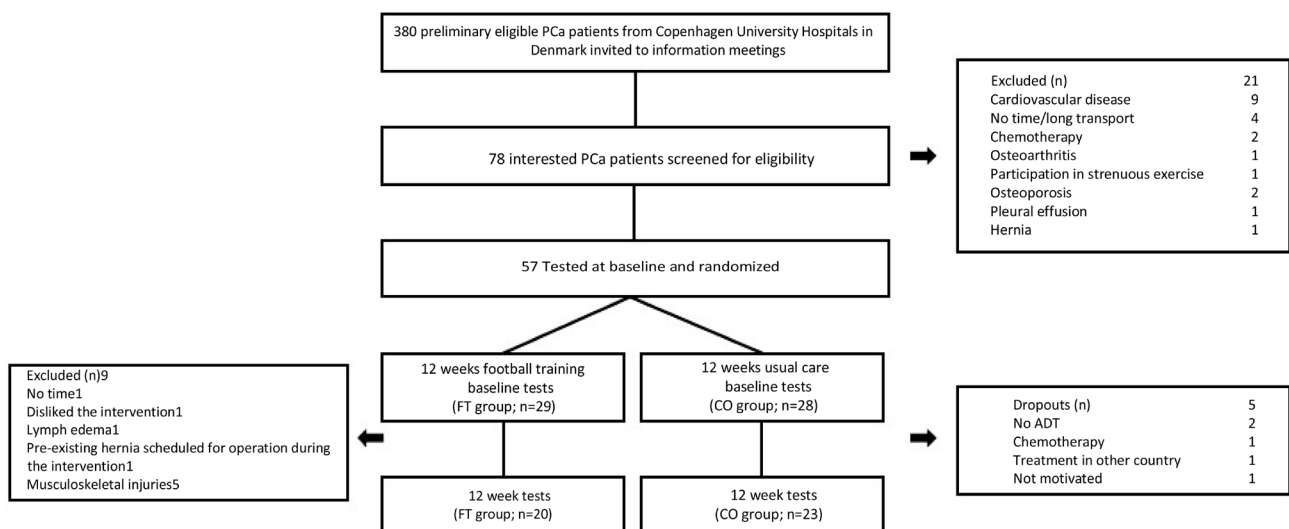


**Figure 1.** Consort diagram with the recruitment process for the study. PCa, prostate cancer; ADT, Androgen deprivation therapy; FT, football training; CO, control.

LV systolic dysfunction and LV diastolic dysfunction, respectively [28] [29] [30]. Tissue Doppler imaging including measurements of LV longitudinal systolic shortening (LVdisplacement) by tissue tracking using 2D colour tissue Doppler and 2D longitudinal global strain (GLS) by speckle tracking were obtained as described previously [31] [32]. Peripheral arterial tonometry measurements of the reactive hyperaemic index (RHI) and the augmentation index adjusted to a heart rate of 75 bpm (AI) were measured using the EndoPat-2000® (Itamar Medical Ltd., Caesarea, Israel) as described previously [14] [27] [33]. Blood pressure (BP) and resting heart rate (RHR) were measured simultaneously 6 times and averaged. Height was measured by a stadiometer, body weight on a digital platform scale and body mass index [kg[m$^2$]$^{-1}$] was calculated. All patients completed an incremental test on a bike and peak oxygen uptake (VO2peak) was determined by pulmonary gas exchange measurements and maximal heart rate (HRmax) was determined.

## 2.3. Statistics

To detect a difference of 0.25 ± 0.26 in mean diastolic E/A ratio and 1.8 ± 1.5 cm s$^{-1}$ in mean peak early diastolic velocity (E') reported between elderly healthy untrained men who participated in a ST intervention and a control group observed in a recent study from our group [16], twelve and (E') and eighteen (E/A) patients in each group were found to be required to detect a similar change with a power of 80% and an alpha level of 0.05. However, the study was multidisciplinary with several other endpoints and the actual power calculation was therefore based on group differences in lean body mass as reported previously [16] [27]. Data were analyzed with SAS® version 9.3. Data were tested for normal distributions and analyzed with descriptive statistic, t-tests, Fishers exact tests, linear associations and analyses of covariance (ANCOVA). All data are presented as absolute means ± standard deviations (SDs) or median (range) (Table 1). All data analyses were based on patients who completed the study (ST group; n = 20, and CO group; n = 23) (Figure 1). The significance level was set at 0.05.

## 3. Results

### 3.1. Patient Characteristics and Study Adherence

The two groups were well balanced except for a lower diastolic BP in the CO group (P = 0.020) (Table 1). In the ST and CO groups, 9 out of 29 (30%) and 5 out of 28 (18%), respectively, did not complete the full intervention period and consequently 43 patients were therefore included in the analyses. The study flowchart and reasons for not completing the study are listed in Figure 1.

### 3.2. Baseline Echocardiography

At baseline, LA diameter was 37 ± 5 mm, LV mass index was 89.1 ± 16.3 g m$^{-2}$, LVEF was 58% ± 6%, and GLS was −19.0 ± 3.9, respectively. No patient had LVEF < 45% and 3 of 43 patients (7%) had LVEF < 50%. LV diastolic dysfunction

**Table 1.** Baseline characteristics of the participants in the football training (FT) and control (CO) groups. Results are means ± SDs, median [range] or number of participants (%). BMI, body mass index; BP, blood pressure; ADT, androgen deprivation therapy; LNRH, luteinizing hormone-releasing hormone.

| | FT group (n = 20) | | CO group (n = 23) | | *P*-values |
|---|---|---|---|---|---|
| | Mean ± SD | Median [range] | Mean ± SD | Median [range] | |
| Age (yrs) | 68.6 ± 7.9 | 72 [44 - 75] | 67.7 ± 4.7 | 68 [55 - 75] | 0.64 |
| Height (cm) | 178 ± 6 | 175 [169 - 190] | 180 ± 6 | 180[172 - 196] | 0.16 |
| Weight (kg) | 85.1 ± 11.5 | 81 [73 - 112] | 89.7 ± 9.9 | 90 [72 - 108] | 0.17 |
| BMI (kg m$^{-2}$) | 27.0 ± 3.0 | 27 [20 - 35] | 27.6 ± 2.4 | 28 [23 - 32] | 0.46 |
| Systolic BP (mmHg) | 131 ± 13 | 129 [109 - 163] | 127 ± 13 | 125 [102 - 160] | 0.34 |
| Diastolic BP (mmHg) | 81 ± 8 | 80 [65 - 105] | 76 ± 7 | 76 [65 - 90] | 0.02 |
| **Prostate cancer specifics** | | | | | |
| Time from diagnosis (months) | 42 ± 44 | 28 [10 - 160] | 46 ± 34 | 37 [12 - 167] | 0.77 |
| ADT treatment (months) | 28 ± 21 | 60 [10 - 104] | 33 ± 16 | 30 [10 - 65] | 0.38 |
| Gleason score | 8 ± 1 | 8 [6 - 124] | 8 ± 1 | 8 [6 - 9] | 0.84 |
| Surgical therapy (% of subjects) | 14/20 (70%) | - | 20/23 (87%) | - | 0.26 |
| Radiation therapy (% of subjects) | 10/20 (50%) | - | 9/23 (39%) | - | 0.68 |
| **Metastases (% of subjects)** | | | | | |
| No metastases | 12/20 (60%) | - | 13/23 (57%) | - | 0.93 |
| Lymph node metastases | 3/20 (15%) | - | 7/23 (30%) | - | 0.29 |
| Bone metastases | 5/20 (25%) | - | 3/23 (13%) | - | 0.44 |
| **Medication** | | | | | |
| LNRH agonist | 20/20 (100%) | - | 23/23 (100%) | - | 1:00 |
| Androgen antagonist | 1/20 (5%) | - | 5/23 (22%) | - | 0.70 |
| Antihypertensive medication | 9/20 (45%) | - | 13/23 (57%) | - | 0.64 |
| Statin | 3/20 (15%) | - | 1/23 (4%) | - | 0.61 |
| Calcium D vitamin supplement | 13/20 (65%) | - | 15/23 (65%) | - | 0.76 |

was present in 30% of all patients, with 85% of these classified as mild and 15% as moderate diastolic dysfunction. E/A ratio and E' were inversely associated with age (r = −0.56, P = 0.0001 and r = −0.38, P = 0.012, respectively).

## 3.3. ST Intervention Characteristics

In the ST group, a total of 28 ST sessions were performed and on average 23 ± 4 (82% ± 16%) were completed. HRmax was 164 ± 14 bpm and ST was performed with an average heart rate of 138 ± 14 bpm (84% ± 4% of HRmax). Specifically, 5% of the total ST time during the intervention was performed at heart rates < 70% of HRmax, and 20% between 70% - 80%, 50% between 80% - 90%, 20% between 90% - 95% and 4% between 95% - 100% of HRmax, respectively.

## 3.4. Effects of ST

### 3.4.1. Cardiac Structure and Function

During the 12 week intervention, LA diameter (P = 0.001) increased in the ST

group and this change was inversely associated with baseline values (P < 0.001). No within or between group differences were observed for other geometric measures of cardiac structure (Table 2).

Twelve-weeks of ST did not induce any within or between group differences in LV or RV systolic function including TDI measurements and GLS (Table 2 and Table 3). After 12 weeks, diastolic variables including E/A ratio (P = 0.030), peak early diastolic velocity (E') (P = 0.016) and E'ColourTDI (P = 0.040) improved in the ST group and these changes were inversely associated with baseline values (P < 0.01). No changes in diastolic variables were observed in the CO group or between groups during the 12 week intervention.

### 3.4.2. VO$_2$ Peak, BP, RHR, and Peripheral Microvascular Function

In the ST group, diastolic BP (P = 0.027) and RHR (P < 0.001) were reduced after 12 weeks with no between group differences compared to CO (Table 4).

Table 2. Standard echocardiographic values at baseline and after 12 weeks in the football training (FT) and control (CO) groups. LVEDD, Left ventricular end-diastolic diameter; LVEDV, LV end-diastolic volume; IVSd, interventricular septal wall thickness; PWT, posterior wall thickness; LV mass index, LV mass adjusted for body surface area; LVEF, LV ejection fraction; MV E velocity, early transmitral inflow; MV A velocity, late transmitral inflow; LA, left atrium. Absolute values are presented as means (SDs) and changes as means (%95 confidence intervals).

| | Baseline | | | | 12 weeks | | | | Change from baseline to 12 weeks | | | | Baseline-adjusted between-group difference in mean change from baseline to 12 weeks | | Fully adjusted* between-group difference in mean change from baseline to 12 weeks | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | FT group | | CO group | | FT group | | CO group | | FT group | | CO group | | | | | |
| Measure | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean (95% CI) | P | Mean (95% CI) | P | Mean (95% CI) | P | Mean (95% CI) | P |
| LVEDD (cm) | 0.23 | 0.04 | 0.23 | 0.03 | 0.23 | 0.03 | 0.23 | 0.04 | 0.04 (−0.19 to 0.26) | 0.753 | 0.02 (−0.19 to 0.23) | 0.867 | 0.01 (−0.24 to 0.26) | 0.955 | −0.01 (−0.28 to 0.25) | 0.911 |
| LVEDV (mL) | 4.09 | 0.92 | 4.17 | 0.96 | 4.09 | 0.92 | 3.92 | 0.84 | 0.3 (−7.6 to 8.3) | 0.931 | −6.2 (−13.6 to 1.2) | 0.099 | 5.8 (−3.9 to 15.6) | 0.02 | 5.8 (−3.4 to 15.0) | 0.208 |
| IVSd (cm) | 0.04 | 0.00 | 0.04 | 0.00 | 0.04 | 0.00 | 0.01 | 0.00 | −0.1 (−0.1 to 0.0) | 0.101 | −0.1 (−0.1 to 0.0) | 0.478 | 0.0 (−0.0 to 0.1) | 0.434 | 0.0 (−0.0 to 0.1) | 0.484 |
| PWT (cm) | 0.07 | 0.01 | 0.04 | 0.07 | 0.07 | 0.01 | 0.07 | 0.01 | −0.00 (−0.07 to 0.07) | 0.997 | −0.05 (−0.12 to 0.02) | 0.124 | 0.03 (−0.03 to 0.11) | 0.295 | 0.04 (−0.04 to 0.11) | 0.344 |
| LV mass index (g m$^{-2}$) | 3.75 | 0.80 | 3.63 | 0.51 | 3.71 | 0.80 | 3.38 | 0.58 | −0.8 (−9.1 to 7.5) | 0.847 | −6.3 (−14.0 to 1.5) | 0.109 | 7.2 (−2.6 to 17.0) | 0.146 | 6.5 (−3.5 to 16.5) | 0.193 |
| LVEF (%) | 2.42 | 0.21 | 2.38 | 0.25 | 2.38 | 0.21 | 2.30 | 0.29 | −1.4 (−4.5 to 1.7) | 0.375 | −1.4 (−4.3 to 1.05) | 0.325 | 1.0 (−2.7 to 4.7) | 0.581 | 1.2 (−2.8 to 5.1) | 0.556 |
| MV E velocity (m s$^{-1}$) | 0.05 | 0.01 | 0.05 | 0.01 | 0.05 | 0.01 | 0.05 | 0.01 | 0.05 (−0.20 to 0.10) | 0.133 | 0.03 (−0.03 to 0.09) | 0.338 | 0.03 (−0.05 to 0.11) | 0.522 | 0.02 (−0.07 to 0.10) | 0.661 |
| MV A velocity m (s$^{-1}$) | 0.06 | 0.01 | 0.05 | 0.01 | 0.05 | 0.01 | 0.05 | 0.01 | −0.03 (−0.10 to 0.03) | 0.327 | 0.01 (−0.05 to 0.07) | 0.808 | 0.01 (−0.07 to 0.08) | 0.887 | 0.02 (−0.05 to 0.09) | 0.573 |
| Mitral inflow E/A ratio | 0.06 | 0.02 | 0.07 | 0.01 | 0.04 | 0.02 | 0.04 | 0.01 | 0.12 (0.01 to 0.22) | 0.030 | 0.02 (−0.08 to 0.12) | 0.724 | 0.06 (−0.08 to 0.19) | 0.385 | 0.05 (−0.07 to 0.18) | 0.385 |
| LA diameter (cm) | 0.13 | 0.00 | 0.13 | 0.00 | 0.13 | 0.00 | 0.13 | 0.00 | 0.3 (0.1 to 0.5) | 0.001 | 0.1 (−0.1 to 0.2) | 0.525 | 0.2 (0.0 to 0.5) | 0.055 | 0.3 (0.0 to 0.5) | 0.080 |
| LA volume (mL) | 2.71 | 0.92 | 2.84 | 0.92 | 2.79 | 0.58 | 2.92 | 0.84 | −1.7 (−13.0 to 9.6) | 0.760 | 2.7 (−7.2 to 12.7) | 0.580 | −5.8 (−16.9 to 5.2) | 0.292 | −5.1 (−17.0 to 6.8) | 0.386 |

**Table 3.** Tissue Doppler imaging echocardiography values at baseline and after 12 weeks in the football training (FT) and control (CO) groups. S', peak systolic velocity; E', peak early diastolic velocity; A', peak late diastolic velocity; S'$_{TDIcolor}$, peak systolic velocity; E'$_{TDIcolor}$, peak early diastolic velocity; A'$_{TDIcolor}$, peak late diastolic velocity; LV displacement, LV systolic longitudinal shortening; GLS, 2D global longitudinal systolic strain. Absolute values are presented as means (SDs) and changes as means (%95 confidence intervals).

| | Baseline | | | | 12 weeks | | | | Change from baseline to 12 weeks | | | | Baseline-adjusted between-group difference in mean change from baseline to 12 weeks | | Fully adjusted* between-group difference in mean change from baseline to 12 weeks | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | FT group | | CO group | | FT group | | CO group | | FT group | | CO group | | FT group | | CO group | |
| Measure | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean (95% CI) | P | Mean (95% CI) | P | Mean (95% CI) | P | Mean (95% CI) | P |
| S' (cm s$^{-1}$) | 8.09 | 1.08 | 8.08 | 1.05 | 8.06 | 1.03 | 9.00 | 1.04 | −0.1 (−0.7 to 0.5) | 0.740 | 0.2 (−0.4 to 0.8) | 0.494 | −0.3 (−1.1 to 0.4) | 0.322 | −0.3 (−1.1 to 0.4) | 0.377 |
| E' (cm s$^{-1}$) | 8.00 | 2.07 | 9.04 | 2.00 | 9.02 | 2.01 | 10.01 | 1.06 | 1.2 (0.0 to2.2) | 0.016 | 0.6 (−0.3 to 1.5) | 0.208 | −0.3 (−1.3 to 0.7) | 0.582 | −0.2 (−1.4 to 0.8) | 0.604 |
| A' (cm s$^{-1}$) | 12.05 | 1.08 | 11.09 | 2.01 | 11.04 | 2.00 | 11.02 | 2.05 | −0.9 (−1.6 to −0.2) | 0.012 | −0.6 (−1.3 to 0.0) | 0.063 | −0.2 (−1.2 to 0.7) | 0.643 | −0.1 (−1.1 to 0.8) | 0.779 |
| S' color$_{TDI}$ (cm s$^{-1}$) | 5.08 | 1.02 | 5.05 | 1.00 | 5.06 | 1.01 | 5.05 | 1.02 | −0.2 (−0.5 to 0.3) | 0.446 | 0.0 (−0.34 to 0.41) | 0.856 | −0.1 (−0.6 to 0.4) | 0.750 | −0.1 (−0.6 to 0.46) | 0.740 |
| E' color$_{TDI}$ (cm s$^{-1}$) | 5.05 | 1.05 | 6.03 | 1.03 | 6.03 | 1.09 | 6.05 | 1.08 | 0.8 (0.0 to 1.5) | 0.040 | 0.0 (−0.7 to 0.8) | 0.911 | 0.5 (−0.6 to 1.6) | 0.373 | 0.5 (−0.6 to 1.6) | 0.354 |
| A' Color$_{TDI}$ (cm s$^{-1}$) | 7.07 | 1.04 | 7.02 | 2.02 | 7.14 | 1.51 | 6.05 | 2.01 | −0.5 (−1.2 to 0.2) | 0.128 | −0.8 (1.5 to 0.1) | 0.027 | −0.4 (−1.3 to 0.5) | 0.344 | −0.5 (−1.4 to 0.4) | 0.292 |
| LV displacement (mm) | 10.09 | 1.04 | 10.05 | 1.07 | 10.06 | 2.01 | 9.09 | 2.04 | −0.2 (−1.1 to 0.7) | 0.592 | −0.7 (−1.5 to 0.2) | 0.114 | 0.5 (−0.7 to 1.8) | 0.368 | 0.7 (−0.5 to 1.9) | 0.256 |
| Global strain (%) | −19.3 | 2.02 | −18.2 | 5.07 | −20.7 | 1.07 | −19.1 | 1.08 | −0.4 (−3.4 to 2.5) | 0.778 | −1.2 (−4.0 to 1.6) | 0.389 | −0.95 (−2.5 to 0.6) | 0.220 | −0.4 (−2.3 to 1.5) | 0.647 |

**Table 4.** Peak oxygen consumption (VO$_2$ peak), blood pressure (BP), resting heart rate (RHR) and peripheral microvascular function at baseline and after 12 weeks in the football training (FT) and control (CO) groups. RHI, reactive hyperemic index; AI, augmentation index. Absolute values are presented as means (SDs) and changes as means (%95 confidence intervals).

| | Baseline | | | | 12 weeks | | | | Change from baseline to 12 weeks | | | | Baseline-adjusted between-group difference in mean change from baseline to 12 weeks | | Fully adjusted* between-group difference in mean change from baseline to 12 weeks | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | FT group | | CO group | | FT group | | CO group | | FT group | | CO group | | FT group | | CO group | |
| Measure | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean (95% CI) | P | Mean (95% CI) | P | Mean (95% CI) | P | Mean (95% CI) | P |
| VO$_2$ peak (L min$^{-1}$) | 2.32 | 0.34 | 2.41 | 0.39 | 2.38 | 0.37 | 2.43 | 0.37 | 0.06 (−0.03 to 0.15) | 0.162 | 0.02 (−0.06 to 0.10) | 0.618 | 0.03 (−0.09 to 0.15) | 0.633 | 0.01 (−0.09 to 0.11) | 0.817 |
| Systolic BP (mmHg) | 131.00 | 13.04 | 127.03.00 | 13.04 | 128.04.00 | 15.09 | 128.07.00 | 15.09 | −2.6 (−6.9 to 1.8) | 0.236 | 1.4 (−2.5 to 5.4) | 0.48 | −3.6 (−9.6 to 2.3) | 0.225 | −2.4 (−8.1 to 3.3) | 0.402 |
| Diastolic BP (mmHg) | 81.01.00 | 8.01 | 75.06.00 | 6.09 | 78.02.00 | 7.09 | 76.03.00 | 6.05 | −3.0 (−5.7 to −0.4) | 0.027 | 0.7 (−1.7 to 3.1) | 0.541 | −1.9 (−5.4 to 1.6) | 0.271 | −1.6 (−5.1 to 1.8) | 0.344 |
| RHR (bpm) | 60.03.00 | 11.04 | 58.00.00 | 8.03 | 56.02.00 | 9.09 | 56.04.00 | 8.09 | −4.1 (−6.4 to −1.8) | 0.000 | −1.5 (−3.6 to 0.5) | 0.143 | −2.2 (−5.1 to 0.8) | 0.141 | −2.1 (−5.0 to 0.7) | 0.141 |
| RHI | 2.35 | 0.047 | 2.19 | 0.04 | 2.29 | 0.57 | 2.30 | 0.045138889 | −0.10 (−0.41 to 0.31) | 0.716 | 0.11 (−0.22 to 0.51) | 0.394 | −0.12 (−0.52 to 0.31) | 0.699 | −0.10 (−0.50 to 0.32) | 0.722 |
| AI | 10.03 | 14.01 | 8.08 | 10.06 | 10.04 | 14.01 | 9.06 | 15.00 | 0.7 (−3.3 to 4.7) | 0.718 | 0.1 (−3.8 to 4.0) | 0.964 | 0.6 (−5.0 to 6.3) | 0.819 | −0.8 (−6.5 to 5.0) | 0.788 |

During the 12 week intervention, no within or between group changes were observed for VO2 peak, systolic BP, RHI and AI.

### 3.4.3. Adverse Events

In the ST group, 2 patients sustained fibular bone fractures during ST session 1 and 16, respectively, and both cases were solo injuries unrelated to tackles or physical contact with other participants. Three patients sustained other injuries, including a partial Achilles tendon rupture (n = 1), a sprained ankle (n = 1), and a strained muscle (n = 1), respectively. All 5 patients fully recovered from these injuries after conservative treatment but were excluded from all the analyses (Figure 1).

## 4. Discussion

To our knowledge, this is the first study to evaluate cardiac structure and function in PCa patients receiving ADT by comprehensive echocardiography before and after a short-term EX intervention. At baseline, considerable cardiac abnormalities were not observed. After 12 weeks, patients randomized to ST displayed significant changes of LA diameter and LV diastolic function in the per-protocol analysis, but no differences were observed in echocardiographic variables between the ST and CO groups. The results suggest that ADT does not have major effects on echocardiographic variables, but may blunt cardiac adaptations to EX.

In men with PCa, ADT is associated with an increased risk of CVD and it is therefore important to determine if cardiac structure and function is attenuated in these patients in absence of overt CVD [3] [7]. Prior to randomization, no considerable structural cardiac abnormality e.g. LV hypertrophy (LVH), was observed in our patients despite that ~50% of patients received antihypertensive medication, which is similar to the percentage of age-matched men treated with antihypertensive agents in the general population [34]. An elevated blood pressure is associated with increased LV afterload which may induce LVH and absence of LVH in our patients is likely to be related to adequate blood pressure control owing to previous long-term medical surveillance associated with ADT. It is, however, interesting that LVH was actually less prevalent in our hypertensive patients compared to hypertensive patients in general and it is possible that ADT may counteract development of LVH in these patients [35] [36]. We also observed a preserved LV systolic function and TDI-derived peak systolic velocity (S'ColourTDI)), and GLS values in our patients were within the normal range, which clearly suggests that subclinical myocardial dysfunction at rest is a rare finding in PCa patients receiving ADT [23] [37]. Aging is associated with reduced resting LV diastolic function mainly because of reduced LV compliance and relaxation [38]. Along this line, we observed lower LV diastolic values (E/A ratio, E'and E' TDIcolour) in older patients and the prevalence of LV diastolic dysfunction was 30% in our study population with a mean age of 68 years. These findings correspond to the prevalence of LV diastolic function in the general

population and suggest that ADT does not accelerate the age-related decline in diastolic function [23] [39].

During the last few years, studies of recreational small-sided ST and other types of EX have demonstrated marked effects on cardiac structure and LV function [14] [16] [22] [40] [41] [42]. A growing body of evidence has also suggested that EX is a powerful intervention to mitigate ADT-related reductions of musculoskeletal and cardiorespiratory functions, but as yet, no study has evaluated the effects of EX on cardiac structure and function in patients receiving ADT [4] [6] [9] [11] [12]. In rodents, chemical orchiectomy has been associated with LV systolic dysfunction which was attenuated by EX [8]. Surprisingly, the present study failed to demonstrate significant changes in cardiac structure or function as measured by comprehensive echocardiography after 12 weeks of ST in patients receiving ADT as compared to controls, even though such intervention has previously been associated with substantial changes of echocardiographic variables in healthy men and men with hypertension or diabetes [14] [16] [41]. In the ST group, we observed an augmented LV diastolic function and increased LA size after 12 weeks, but these changes were influenced by lower baseline values and were not significantly different from the response in the CO group.

Notably, improvements of $VO_2$ peak were also absent after 12 weeks of ST in our study and it is possible that this attenuated response as compared to increased $VO_2$ peak observed after ST in other patient subsets e.g. men with hypertension or diabetes, was related to the lack of changes in cardiac structure and function [14] [17]. On the other hand, other types of EX training e.g. cycling, jogging or combined aerobic and resistance training have been found to improve aerobic fitness in many, but not all, studies of men with PCa receiving ADT, whereas absence of between group differences in BP after EX in our patients is in line with the findings of others [4] [6] [9] [10] [11] [12] [43]. The EX training modality is likely a major determinant of the improvement of $VO_2$ peak and cardiac adaptations and emerging evidence has indicated that in this regard, high-intensity interval training may be more efficient than moderate-intensity continuous EX e.g. in previously sedentary subjects or patients with heart failure or coronary artery disease, respectively [20] [21] [44]. Indeed, we have found that ST, which is akin to high-intensity interval training, was more effective than running to achieve increased $VO_2$ peak and other cardiovascular adaptations in sedentary women [22]. In addition to our observations in men with hypertension and diabetes, we have also observed marked cardiovascular effects including increased $VO_2$ peak after ST in healthy untrained 65 - 75 year-old men without soccer experience and in veteran soccer players with life-long participation in ST [14] [17] [42]. In the present study, men with PCa receiving ADT achieved similar high heart rates during ST as we have observed in other subjects reported in our previous studies, and the absence of changes in $VO_2$ peak and cardiac structure and function, respectively, therefore clearly suggest that ADT can counte-

ract favourable cardiovascular effects of high-intensity interval training.

We measured microvascular endothelial function by use of peripheral arterial tonometry, which is a noninvasive, automated and operator-independent method that is easy to perform compared to other methods used to evaluate endothelial function e.g. invasive protocols or ultrasound measurements of flow-mediated vasodilation of the brachial artery [16] [33]. Microvascular endothelial function has been suggested to be more sensitive to cardiometabolic risk factors e.g. body mass index and diabetes mellitus, and may display abnormalities dependent on such risk factors earlier than measures of conduit artery endothelial function [33]. Importantly, endothelial dysfunction measured by these noninvasive techniques is an independent risk factor of CVD and physical activity can attenuate the general age-related decline in endothelial function and nitric oxide bioavailability [45] [46]. While we are not aware of previous studies of microvascular endothelial function in this setting, EX was recently associated with improved endothelial function measured by flow-mediated brachial artery vasodilation in PCa patients not receiving ADT [47]. In our study, however, 12 weeks of ST did not elicit significant changes in peripheral microvascular function. This is finding is in line with results of other studies with peripheral arterial tonometry after ST and other types of EX and, taken together, these data suggest that microvascular endothelial function is not augmented by short-term EX [14] [48] [49].

In a recent publication from the present study cohort, ST was found to be experienced by patients as a feasible and enjoyable exercise modality that was associated with a sense of regained control over their health and promotion of a mutually caring behaviour between subjects [16] [50]. Although we observed a number of musculoskeletal injuries, such injuries must be weighed against the psychological benefits and the detrimental effects of physical inactivity and consequent morbidity and mortality.

A number of limitations apply to the present study. The study was small-scale, it only examined effects of ST [not other EX modalities] and the study population was exposed to selection bias e.g. the intervention preferentially attracted interested patients capable of performing exercise training. The lack of a control group of PCa patients not receiving ADT, measurements of conduit artery endothelial function and assessment by stress echocardiography are also among the limitations of the study. Moreover, long-terms effects and effects of ST on clinical endpoints were not examined.

## 5. Conclusion

In men with PCa receiving ADT, considerable echocardiographic abnormalities at rest were not observed, whereas 12 weeks of ST failed to elicit significant cardiovascular adaptations. The results suggest that ADT is not associated with significant effects on cardiac structure and function, but that such treatment may blunt cardiovascular adaptations to short-term exercise training.

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## Conflict of Interest

None Declared.

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