Left Ventricular Strain and Strain Rate Responses to Submaximal Exercise in Prostate Cancer Patients Treated with Androgen Deprivation Therapy

by

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Abstract

Background: Androgen Deprivation Therapy (ADT) is a commonly used treatment for prostate cancer with controversy currently surrounding its association with long-term cardiovascular disease risk. Therefore, the aim of the current investigation was to non-invasively measure left ventricular mechanics at rest and during submaximal exercise in human prostate cancer survivors with and without a history of ADT.

Methods: Eighteen prostate cancer survivors, 9 with a history of ADT and 9 matched (1:1) non-ADT controls, completed the protocol. Standard and tissue Doppler echocardiography were used to evaluate left ventricular systolic and diastolic function at rest and during submaximal cycling exercise.

Results: At rest, there were no differences between groups. Ejection fraction was not different between groups at rest or during exercise (rest p=0.7; exercise p=0.8). During exercise, systolic left ventricular longitudinal strain and strain rate failed to increase in the ADT group (p=0.4; p=0.07), but significantly increased in the non-ADT group (p=0.03; p=0.02). During exercise, systolic strain was significantly different between groups (p=0.02). Diastolic longitudinal strain increased with exercise in both groups (p=0.003; p=0.003). In the ADT group during exercise, mitral valve deceleration time was not significantly different from rest (p=0.8) and was slower compared to non-ADT (p=0.03).

Conclusion: In prostate cancer survivors with a history of ADT, there are significant abnormalities of left ventricular systolic function that become apparent with exercise. These findings may hold significant value beyond the standard resting characterization of ventricular function, in particular as part of a risk-stratification strategy.

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Chapter 1 - Introduction

Prostate cancer is the most common non-skin cancer among American men, with approximately 1 in 9 men diagnosed with prostate cancer during their lifetime (28), resulting in an estimated 3.5 million new cases over the next 20 years. Currently, the standard treatment recommendations for prostate cancer consists of some combination of surgery, radiation therapy, and/or androgen-deprivation therapy (ADT). ADT targets testosterone, the main androgen that stimulates prostate cancer cell growth, and can inhibit post-surgical growth or diminish the size of the tumor in some patients (17). As such, ADT is commonly prescribed for prostate cancer with nearly 40-50% of patients receiving ADT within the first six months post-diagnosis (23) with treatment lasting 2 to 3 years (3).

Despite the effectiveness of ADT, possible side effects related to ADT and long-term cardiovascular disease (CVD) morbidity and mortality may occur (16). Evidence from several studies suggest that ADT-induced hypotestosteronemia increases cardiac morbidity by 20% in the first 12 months of treatment (12, 13, 21). Additionally, ADT has been associated with changes in CVD risk factors, including: visceral adiposity, insulin resistance, decreased high-density lipoprotein, increased low-density lipoprotein, and increased triglycerides (21). Recently, Keating et al. (13) found that prior ADT was associated with an 11% increased risk of myocardial infarction (MI), 16% increased coronary heart disease risk, and a 16% increased risk of sudden cardiac death. Conversely, Nguyen et al. (18) found no difference in long- or short-term CVD death in prostate cancer patients with a history of ADT compared to non-ADT controls. In their study the ADT treated men also had lower rates of Prostate Cancer-Specific Mortality, and a lower all-cause mortality, as compared to other treatment groups. These findings

were further supported by Efstathiou et al. (4) who observed a lower CVD mortality (8.4% vs 11.4%) in men receiving a luteinizing hormone-releasing hormone (LHRH) agonist, such as Leuprolide. Due to the significant controversy (16) and potential clinical concerns over this issue, additional work is needed to determine the interaction between ADT and cardiovascular health.

Echocardiographic assessment of myocardial deformation, specifically left ventricular (LV) strain and strain rate, is an emerging non-invasive method used for detecting subclinical ventricular dysfunction and has been shown to provide significant prognostic value in many patient populations (6, 27). Thus, evaluation of LV strain and strain rate provides a non-invasive method to both evaluate and monitor changes in CVD risk in prostate cancer survivors treated with ADT, which to our knowledge has not been previously investigated. Therefore, the primary aim of the current study was to investigate non-invasive measurements of LV function in prostate cancer survivors with and without a history of ADT. It was hypothesized that prostate cancer patients with a treatment history including ADT would have decreased LV systolic and diastolic functional parameters (e.g., velocities, mitral valve parameters, strain, and strain rate) compared to non-ADT controls at rest. Since exercise as a stressor reveals LV dysfunction that can be obscure at rest (15), we further hypothesized that during exercise, these functional parameters would remain unchanged in response to exercise in the ADT treated patients resulting in significant differences between ADT and non-ADT patients.

Chapter 2 - Methods

Study Design and Participants

The present study utilized a case-control cross-sectional study design. Prostate cancer survivors were assigned to either an ADT or non-ADT group, based on their cancer treatment history. A total of 9 prostate cancer survivors with a history of ADT were screened for eligibility and enrolled into the study (ADT group). These ADT treated patients were propensity score matched (1:1) with a control group consisting of prostate cancer survivors with no history of ADT (non-ADT group) based on age, body mass index (BMI) and submaximal exercise capacity. Patients were excluded from participation if they had any of the following: uncontrolled hypertension, unstable angina, diabetes, known atherosclerotic CVD, uncontrolled cholesterol, current smoker, or history of myocardial infarction. Some participants were taking antihypertension medications (ADT, n=8; non-ADT n=3) and statins (ADT, n=3; non-ADT n=6), but at similar proportions between groups. To increase ecological validity and minimize acute changes in systemic cardiovascular function associated with drug withdrawal, these medications were not withheld before testing. All procedures were approved by the Kansas State University Institutional Review Board for research involving human subjects, and all standards conformed to the Declaration of Helsinki.

Experimental Procedures

All testing was conducted following a >4 hr fast in a temperature-controlled clinical environment (~20°C–22°C). All patients underwent a preliminary introductory session to obtain

written informed consent, physician approval, and completion of a general health history questionnaire. Following physician approval, LV mechanics and sub-maximal cardiorespiratory exercise performance were assessed on a subsequent visit. Testing order was not randomized with assessments of LV function always preceding the graded cardiorespiratory exercise test.

2-dimensional and tissue Doppler echocardiography. Each participant was placed supine on an echocardiographic table that utilizes a unique tilt function to place the patient into the 45° left-lateral decubitus position, while supporting the torso, hips, and legs. Patients were instrumented for continuous beat-by-beat systolic, diastolic, and mean blood pressure (SBP, DBP, and MAP, respectively) measurements via calibrated continuous finger plesmythography (Finometer Pro; Finapress Medical Systems, Amsterdam, The Netherlands). A three-lead echocardiogram (ECG) was used to continuously measure heart rate (HR). Following a 5 min acclimation period, transthoracic echocardiography was performed at rest and during exercise by an experienced sonographer, according to the standards of the American Society of Echocardiography using a commercially available system (Vivid S6 BT12; GE Healthcare) with a 1.5- to 4.3-mHz phased array transducer. Exercise consisted of a 20 W min^{-1} ramped cycle on a supine bicycle ergometer (Lode Angio, Groningen, Netherlands) used to increase heart rate to 100 beats per minute, which was then maintained throughout the test. Breath-by-breath pulmonary ventilation and gas exchange data were continuously measured (Ultima CPX, Medical Graphics Corp.,MN, USA) and averaged across the resting baseline and during steady-state exercise.

For a given participant, LV systolic and diastolic function were derived via apical 4-chamber two-dimensional images. For all LV measurements the average of three consecutive cardiac cycles were used. LV volumes were quantified at end-systole (ESV) and end-diastole (EDV) via the perpendicular axis from the apex to the distal boundary of the mitral valve (MV) leaflets. LV ejection fraction (LVEF) was calculated as LVEF = [(EDV-ESV)/EDV] × 100. Stroke volume (SV) and cardiac output (Q) were calculated as SV = ESV – EDV and Q = SV x HR, respectively. MV early filling (E) and atrial filling (A) peak velocities, E/A ratio, and E-wave deceleration time (MVdecT) were measured via pulse-wave Doppler from the transmitral flow with the sample volume placed between the MV leaflets. The peak systolic (Sm), early diastolic (Em), and late diastolic (Am) mitral annular velocities of the septal wall were measured via color tissue Doppler in the apical 4-chamber view at a constant rate of 100 frames/s using a narrow sector and high frame rate and by placing the sample volume in the basal segment of the interventricular septum.

Peak LV tissue Doppler longitudinal strain and strain rate were obtained from derived from 2-dimensional apical images and analyzed using the software incorporated in the Vivid S6 system as previously described (24). In each patient, the sonographer ensured longitudinal movement was in direct line with the ultrasound beam. Sample volumes were placed along the basal, mid-, and apical LV segments of the septal wall and averaged to give a mean value for the entire septal wall. From this, longitudinal myocardial function was evaluated using peak systolic strain, peak systolic strain rate, and early filling strain rate averaged across three consecutive cardiac cycles. Briefly, LV strain provides a dimensionless measure of ventricular myocardial fiber *deformation* during the cardiac cycle relative to its initial length (i.e., reported as

percentage). Strain rate (the first derivative of strain) is the *rate of myocardial deformation* during systolic and early filling periods of the cardiac cycle (11).

Graded Cardiopulmonary Exercise Test. Upon completion of the echocardiographic examination, each patient was given 15-20 min recovery period followed by a symptom-limited, ramped, incremental exercise protocol on a semi-recumbent cycle ergometer to determine their submaximal aerobic exercise capacity (Lode, Corival). Following a 5-min resting baseline, subjects pedaled at 50–60 rpm with progressive increases in power output at a rate of 20 W min^{-1} until the patient reached 85% of their age-predicted heart rate. Breath-by-breath pulmonary ventilation and gas exchange data were continuously measured (Ultima CPX, Medical Graphics Corp., MN, USA) and averaged into 15 second mean values. The pulmonary oxygen uptake (VO_2) at the gas exchange threshold (GET) was used as a submaximal index of exercise capacity as it demarcates the boundary between moderate and heavy exercise intensity domains (1). The obtainment of the GET was determined as the oxygen uptake (VO_2) at which the carbon dioxide output (VCO_2) increased out of proportion with respect to VO_2 and there was an increase in ventilation/oxygen uptake (VE/VO_2) with no increase in VE/VCO_2, as previously described (2). Due to the absence of a physician, population age, and potential risk of adverse responses, incremental tests to maximum effort could not be performed.

Statistical Analysis

All statistical analyses were performed by using SigmaStat 2.0 (Jandel Scientific, San Rafael, CA). All continuous variables are reported as mean ± SD unless otherwise stated. To determine the influence of ADT history (group) and exercise on 2-dimensional and tissue Doppler echocardiography variables a two-way repeated-measures ANOVA was performed, with significant changes in the within and between groups evaluated via a post hoc Student-Newman-Keuls test. Differences were considered statistically significant when $P \leq 0.05$.

Chapter 3 - Results

Demographic and clinical parameters for ADT and non-ADT groups are presented in Table 1. There were no differences in age, height, mass, and BMI between groups. GET was not different between groups. Cancer staging between the ADT and non-ADT groups are as follows: (Stage 1-2: ADT n=5, non-ADT n=8); (Stage 3-4: ADT n=4, non-ADT n=1). Three patients in the ADT group and seven patients in the non-ADT group had a prostatectomy procedure. Two ADT patients were treated via Combined Androgen Blockade which utilizes Leuprolide with Bicalutamide (LHRH agonist plus an antiandrogen, respectively) to block multiple pathways of testosterone production. Total serum testosterone levels were significantly different between groups (Table 1).

2-dimensional and tissue Doppler echocardiography. Heart rate, SBP, DBP, and MAP responded similarly between groups in response to exercise (Table 2). Rate Pressure Product (RPP) and was used to define myocardial work and was not significantly different between groups at rest or exercise. Similarly, pulmonary VO_2 was not different between groups during exercise. LVEF, EDV, and ESV were not different at rest nor exercise when comparing the ADT to non-ADT groups (Figure 1). Stroke volume and cardiac output increased to a similar extent in response to exercise with each group.

MVdecT was not different at rest when comparing ADT and non-ADT groups. In the ADT group, MVdecT did not change from rest to exercise. However, in the non-ADT group, MVdecT was significantly faster during exercise compared to rest, which was also significantly faster than the ADT group during exercise (Figure 2). Peak MV E-wave velocity and A-wave

velocity increased with exercise in both groups, with no differences between groups. In both groups, the E/A ratio significantly changed from rest to exercise and was not different between groups.

Tissue Doppler echocardiographic measurements of LV systolic and diastolic function are presented in Table 3 and Figure 3. LV longitudinal septal wall systolic strain was not different at rest between ADT and non-ADT groups (Figure 3A, $p = 0.9$). However, in response to exercise the non-ADT group observed a significant increase in longitudinal strain from rest ($p = 0.03$) that was not observed in the ADT group ($p = 0.4$). The longitudinal strain during exercise was significantly lower in the ADT group compared with non-ADT subjects ($p = 0.02$). At rest, LV septal wall longitudinal strain rate in systole (SRsys) and early filling (SRe) were not different between groups (SRsys: $p = 0.9$; SRe: $p = 0.8$) (Figure 3). In the ADT group, SRsys did not significantly change from rest to exercise ($p = 0.07$). However, in the non-ADT group, SRsys increased from rest to exercise by 28% (SRsys: $p = 0.02$). In both groups, SRe significantly changed from rest to exercise (ADT $p = 0.003$; Non-ADT 0.003). However, SRe was not significantly different between groups (Rest $p = 0.8$; Exercise $p = 0.8$). Sm, Em, and Am were not different at rest or exercise between groups.

Chapter 4 - Discussion

The present investigation evaluated LV function, with noninvasive imaging techniques, at rest and submaximal exercise in prostate cancer survivors with a history of ADT and demonstrated a variety of abnormalities, particularly with exercise. These include a negatively impacted LV systolic strain, systolic strain rate, and MVdecT, in the ADT group in response to exercise compared to prostate cancer survivors not treated with ADT. These data confirm our hypothesis that prostate cancer patients with a history of ADT have decreased LV systolic and diastolic function in response to an increased myocardial work via exercise compared non-ADT patients. However, these findings do not support our hypothesis that prostate cancer patients with a history of ADT will have decreased LV systolic and diastolic functional parameters compared to non-ADT controls at rest. Given the clinical utility of LV strain and strain rate imaging (25), particularly during exercise (26), these findings suggest important clinical information is be gained during submaximal exercise in prostate cancer survivors with a history of ADT that cannot be obtained at rest.

The impact of previous ADT and its association with long-term CVD morbidity and mortality risk remain controversial (16). However, the present investigation shows that myocardial changes are present in prostate cancer survivors who have underwent ADT (Figure 3). According to Saigal et al. (2007), ADT-induced hypotestosteronemia increases cardiac morbidity by 20% in the first 12 months of treatment (21). Further, Keating et al. (2006) indicated an increased risk for myocardial infarction, coronary heart disease, and sudden cardiac death with ADT (13). Conversely, Efstathiou et al. (2009) observed a 3% decreased CVD mortality in men with a history of ADT (4). Because of this significant controversy from these

retrospective epidemiological studies and potential clinical implications, we performed a set of experiments to determine if prior ADT in prostate cancer survivors altered subclinical measurements of LV function at rest and exercise. As such, the present investigation shows men previously treated with ADT for an average treatment duration of 29 months had significantly different LV responses to submaximal exercise when compared to a group of match non-ADT cancer survivor controls. These present findings lend support to the idea of a potential adverse relationship between ADT and long-term cardiovascular health.

Routine clinical parameters of myocardial function such as LVEF have important limitations when attempting to evaluate early changes in subclinical myocardial function (10). Specifically, changes of $\geq$10% in LVEF are required to adequately detect differences and, therefore this measure may not be sensitive enough nor completely reflect sub-clinical systolic dysfunction (19, 27). Furthermore, LVEF only provides information on systolic dysfunction, which is concerning given the increased recognition of LV diastolic dysfunction in several clinical populations (20). As such, recent studies have demonstrated the clinical importance of myocardial deformation imaging for evaluating regional systolic and diastolic function as markers of early myocardial changes to provide valuable insight into the development of subsequent CVD onset (27). For example, Thavendiranathan et al. (2014) reviewed the efficacy of myocardial strain imaging for the early detection of cardiotoxicity following cancer chemotherapy (27). They report that LV strain and strain rate demonstrated a range of dysfunctional reductions in myocardial function from 9% to 20% and confirm that these changes occur prior to changes in LVEF. Thus, this recent evidence highlights the potential prognostic

value of echocardiographic myocardial deformation parameter measures for the evaluation of subclinical myocardial dysfunction.

The present study takes important steps in exploring the utility of non-invasive myocardial deformation imaging in the evaluation of the long-term cardiac effects associated with ADT in prostate cancer survivors. Importantly, we established that decreases in parameters of myocardial deformation could occur independent of changes in LVEF in this population. Similar to the findings of Thavendiranathan et al. (2014) investigating anthracycline-chemotherpy induced cardiotoxicity, prostate cancer survivors with a history of ADT experience a degree of LV systolic dysfunction, even in the context of a normal LVEF (27). Additionally, as described by Lancellotti et al. (2016), exercise as a stressor reveals myocardial mechanical abnormalities and dysfunction, that are otherwise obscure at rest (15). We utilized an exercise echocardiography protocol from Tan et al. (2009) that clamped each subject to a submaximal HR of 100BPM, given that many echocardiography parameters are heart rate dependent (26). Additionally, matching heart rate resulted in a similar myocardial oxygen consumption (i.e., RPP) between groups, which allowed for comparisons of strain and strain rate to be drawn between groups (14). From this exercise protocol, we observed that men with a history of ADT demonstrated a lack of change in LV systolic strain and strain rate from rest to exercise, whereas, the non-ADT controls observed the typical (26) significant increase in systolic strain and strain rate with exercise. This indicates that men who have a history of ADT may be experiencing a variety of systolic LV abnormalities that are only manifest in response to mild increases in myocardial work (i.e., exercise). This altered strain and strain rate response is therefore

suggestive of an impaired contractile performance within the cardiomyocytes often associated with systolic dysfunction (25, 31).

In addition to the changes in LV systolic function, the present investigation also demonstrated differences in MVdecT between the ADT patients and non-ADT controls, indicating some degree of LV diastolic dysfunction. According to Garcia et al. (1998), a delayed relaxation (i.e., increased MVdecT) often occurs in patients with stage 1 diastolic dysfunction (5). These patients typically have a reduced LV relaxation rate and are usually asymptomatic. In the present study, additional markers of diastolic function such as the E/A ratio and strain rate in early filling, were not different between groups, suggesting that the association with LV diastolic abnormalities in those with ADT history may be minor.

Mechanistically the adverse effects of ADT on myocardial function are well supported in animal models. Tsang et al. (2008) utilized isolated animal hearts to determine that hypotestosteronemia significantly alters LV diastolic pressures and systolic/diastolic myocardial velocities (29). Furthermore, male rodents with induced hypotestosteronemia experience a 34% reduction in calcium-myosin adenosine triphosphate-ase (ATP-ase) activity which was used as a marker of cardiomyocyte contractile performance, along with reductions in LVEF, peak systolic pressure, and myocardial oxygen consumption (22). Similarly, Golden et al. (2004) observed a twofold dysfunctional increase in myosin heavy chain-B transcripts and an 80% decrease in myosin heavy chain-A transcript levels in the rodent heart following hypotestosteronemia (9). These dysfunctional changes were associated with a 16% increase in time to peak shortening, an 18% increase in relaxation time and an 80% decrease in sodium/calcium pump gene expression

(8). These findings, coupled with the controversial clinical CVD outcome data in human prostate cancer survivors, highlights how complex and limited our understanding of long-term cardiovascular health in prostate cancer survivors is in those treated with ADT.

Implications and Experimental Considerations

With current biomedical technology, measures of regional deformation and contractile function are appropriate for the clinical setting and may provide valuable prognostic information that can be used to guide various preventative strategies (25). As the present study demonstrates, detecting pre-symptomatic cardiac abnormalities can be achieved, particularly with submaximal exercise, and appears to be critical for assessing preclinical cardiac abnormalities in patients undergoing long-term therapeutic cancer treatments such as ADT. This data suggests that men with a history of ADT may have myocardial abnormalities at mild levels of exercise. Evaluating these patients may require exercise to determine underlying dysfunction that remains unseen while the individual is at rest.

Several experimental limitations should be considered when interpreting the study findings. First, the cross-sectional nature of the present study precludes definitive assessment of the direct effects of ADT on LV function. However, it does provide some of the first evidence of sub-clinical LV systolic dysfunction during exercise in this population. In the present study, all patients continued their normal medications throughout their participation in this study, which may have impacted the results. According to Wang et al. (2008), the use of antihypertensive drugs would be expected to improve symptomatic cardiovascular responses; therefore, given that

antihypertensive drugs were primarily taken by the ADT group, the significant difference between groups in the current study may have been potentiated had medications been withheld (30). There was also a range of times since prostate cancer diagnosis for the patients enrolled in the current study, with the ADT group having a range of 6-219 months and the non-ADT group had a range of 1-223 months. According to results from Keating et al. (2013) men treated with ADT within 252 months (21 years) of diagnosis remain at a greater risk of myocardial infarction compared to non-ADT controls (12). Furthermore, regarding the total time receiving ADT for the present study, the ADT cohort had a range of 3-84 total months of treatment, which is similar to that of Gilbert et al. (2013) who reported decreased in cardiovascular function in men receiving ADT with a range of 6-133 total months of treatment (7).

In conclusion, this is the first investigation, to our knowledge, to demonstrate a combination of dysfunctional LV systolic and diastolic parameters in the prostate cancer group with a history of ADT in response to submaximal exercise. These decreases in LV mechanics suggest that a history of ADT may have an adverse effect of cardiac function, which may contribute to the increased long-term risk of cardiovascular disease morbidity and mortality associated with cancer treatment. However, future work will be required to determine if these measures, at rest and during exercise, will be a useful parameter for the prediction of long-term CVD development. Furthermore, longitudinal measurements of these parameters may be clinically useful for monitoring prostate cancer patients during, and in the years following, ADT.

Table 1 – Demographic and clinical characteristics

Table 1. Demographic and clinical characteristics

	ADT	Non-ADT	p Value
Age (years)	68 ± 8	65 ± 3	0.16
Height (cm)	179 ± 9	176 ± 5	0.3
Mass (kg)	92 ± 8	87 ± 12	0.4
BMI (kg/m^2)	28.7 ± 4	28 ± 4	0.8
GET (ml/kg/min)	14.3 ± 2.9	13.9 ± 2.7	0.7
Months since diagnosis	75 ± 70	85 ± 80	0.8
Months on ADT	29 ± 32	-	
Leuprolide cumulative dose (mg)	209 ± 223	-	
Bicalutamide (mg)	425 ± 106	-	
Testosterone level (ng/dl)	63 ± 146	407 ±168	0.04
Radiation	5	2	0.1

BMI, body mass index; GET, gas exchange threshold;

Table 2 - Hemodynamic Variables

Table 2. Hemodynamic Variables

	ADT Patients (Rest)	ADT Patients (100 BPM)	p Value (ADT rest vs 100 BPM)	Non-ADT Patients (Rest)	Non-ADT Patients (100 BPM)	p Value (Non-ADT rest vs 100 BPM)	p Value (ADT vs Non-ADT)
Heart rate (BPM)	65 ± 12	103 ± 4	<0.001	72 ± 7	103 ± 4	<0.001	0.08[r] 0.9[e]
Systolic BP (mmHg)	139 ± 19	184 ± 14	<0.001	142 ± 17	174 ± 25	<0.001	0.8[r] 0.2[e]
Diastolic BP (mmHg)	68 ± 10	85 ± 7	<0.001	76 ± 8	89 ± 11	0.001	0.1[r] 0.4[e]
MAP (mmHg)	93 ± 13	121 ± 9	<0.001	101 ± 11	120 ± 18	<0.001	0.3[r] 0.9[e]
RPP (BPM x mmHg)	9231 ± 2723	18909 ± 1565	<0.001	10291 ± 1888	17838 ± 2590	<0.001	0.4[r] 0.3[e]
Pulmonary VO_2 (l/min)		1.1 ± 0.2			0.9 ± 0.3		 0.1[e]

mean±SD. [r] comparison between ADT and non-ADT at rest. [e] comparison between ADT and non-ADT during exercise. BP, blood pressure; MAP, mean arterial pressure; RPP, rate pressure product; VO_2, rate of oxygen consumption;

Table 3 - Echocardiography

Table 3. Echocardiography

	ADT Patients (Rest)	ADT Patients (100 BPM)	p Value (ADT rest vs 100)	Non-ADT Patients (Rest)	Non-ADT Patients (100 BPM)	p Value (Non-ADT rest vs 100 BPM)	p Value (ADT vs Non-ADT)
LVEF (%)	64 ± 0.07	67 ± 0.05	0.08	63 ± 0.05	67 ± 0.06	0.06	0.7[r] 0.8[e]
Cardiac output (l/min)	4.5 ± 1.2	7.9 ± 1.7	<0.001	4.7 ± 0.6	7.6 ± 1.4	<0.001	0.8[r] 0.6[e]
MV Deceleration Time (ms)	203 ± 62	218 ± 71	0.8	224 ± 65	142 ± 36	0.01	0.6[r] 0.03[e]
MV E-wave velocity (cm/s)	61 ± 17	106 ± 13	<0.001	65 ± 18	90 ± 20	<0.001	0.3[r] 0.06[e]
MV A-Wave Velocity (cm/s)	67 ± 17	92 ± 20	0.004	68 ± 17	83 ± 27	0.03	0.8[r] 0.6[e]
MV E/A Ratio	0.96 ± 0.4	1.19 ± 0.2	<0.001	0.96 ± 0.1	1.12 ± 0.3	0.02	0.7[r] 0.7[e]
Sm (cm/s)	7.03 ± 1.8	10.4 ± 2.1	0.02	8.5 ± 2.6	9.03 ± 2.1	0.8	0.2[r] 0.4[e]
Em (cm/s)	7.97 ± 1.8	10.6 ± 1.2	0.07	8.2 ± 2.1	11 ± 3.1	0.2	0.6[r] 0.9[e]
Am (cm/s)	7.6 ± 1.8	10.2 ± 3.3	0.1	9.6 ± 2.7	10 ± 2.6	0.7	0.1[r] 0.8[e]

mean±SD. [r] comparison between ADT and non-ADT at rest. [e] comparison between ADT and non-ADT during exercise.

LVEF, left ventricular ejection fraction; MV, mitral valve; E-wave, early transmitral flow velocity; A-wave, late transmitral flow velocity; Sm, peak systolic myocardial mitral annular velocity by color tissue Doppler imaging; Em, peak early diastolic myocardial mitral annular velocity by color tissue Doppler imaging; Am, peak late diastolic myocardial mitral annular velocity by color tissue Doppler imaging;

Figure 1 - Left ventricular systolic and diastolic volumes from rest to exercise in the ADT and non-ADT groups. Mean and individual LV end diastolic volume (A), end systolic volume (B), and stroke volume (C). * denotes significant difference from rest to exercise**.**

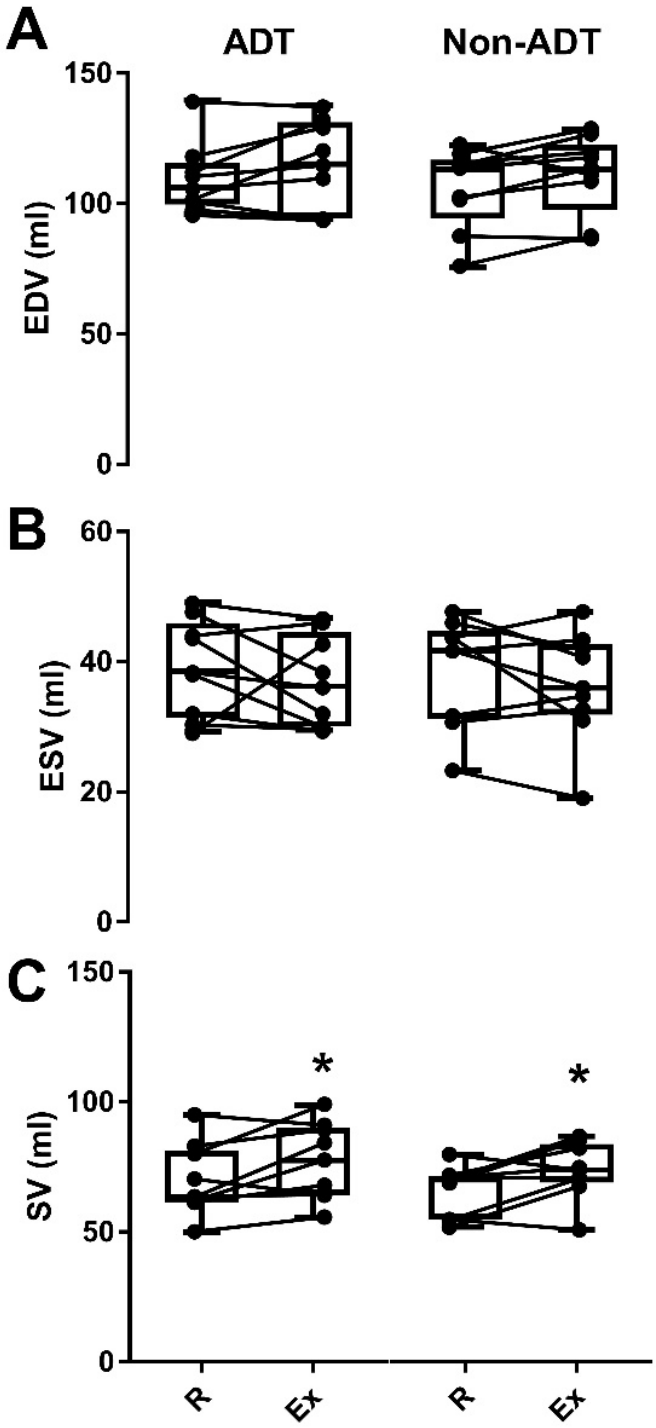


Figure 2 - Mitral Valve deceleration time from rest to exercise in the ADT and non-ADT groups. Mean and individual mitral valve deceleration time. * denotes significant difference from rest to exercise. + denotes significant difference between groups

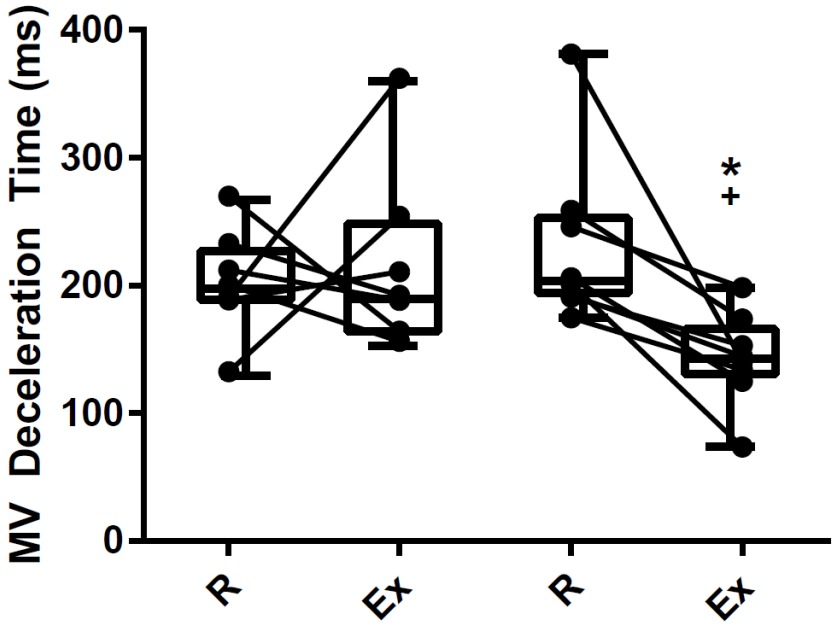
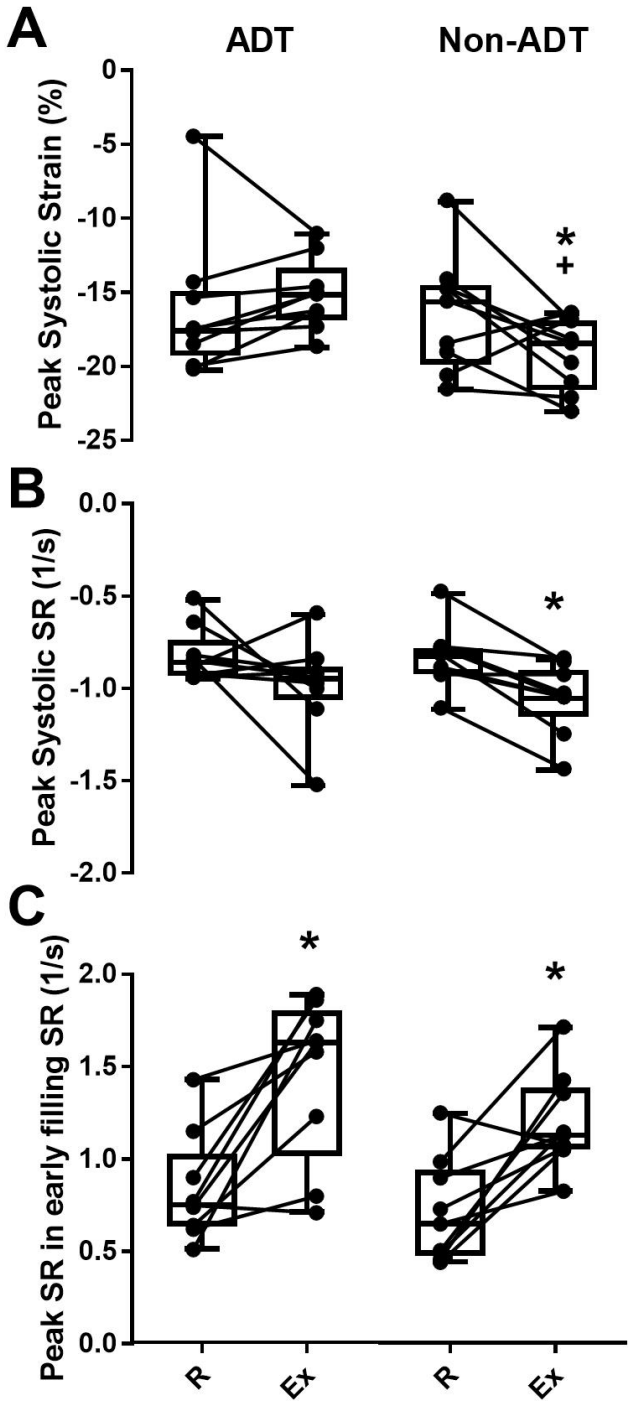


Figure 3 - Left ventricular systolic and diastolic function from rest to exercise in the ADT and non-ADT groups. Mean and individual LV septal wall systolic strain (A), strain rate in LV systole (B), and strain rate in LV early filling diastole (C). * denotes significant difference from rest to exercise. + denotes significant difference between groups



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