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Altered Stress Hormone Response Following Acute Exercise During Prostate Cancer Treatment

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Abstract

Exercise training reduces the side effects of cancer treatments, however, the stress hormone response to acute exercise during prostate cancer (PCa) treatment is unclear. **PURPOSE**: To examine the effects of acute exercise on circulating cortisol, epinephrine (Epi), and norepinephrine (NE) concentrations during PCa treatment with and without androgen deprivation therapy (ADT). **METHODS**: Men with PCa (n=11), with PCa on ADT (n=11) and non-cancer controls (n=8) had blood samples for stress hormones collected before and immediately (0h), 2h, and 24h after 45 minutes of intermittent cycling at 60% of peak wattage. **RESULTS**: NE increased by 385% ($p<0.001$) at 0h and remained elevated at 2h ($p<0.05$) with no group differences. Overall, cortisol significantly increased at 0h (36%, $p<0.012$) and then significantly decreased below baseline at 2h (-24%, $p<0.001$) before returning to resting levels at 24h. Cortisol levels during ADT were 32% lower than PCa ($p=0.006$) with no differences vs. controls. Epi increased immediately after exercise more in controls (817%, $p<0.001$) than with ADT (700%) and PCa (333%) patients and both cancer groups absolute levels were attenuated relative to controls (ADT: -54%, PCa: -52%, $p=0.004$). **CONCLUSIONS**: Compared with age-matched controls, PCa and ADT patients exhibited similar stress hormone responses with acute exercise for NE and cortisol but an attenuated EPI response that suggests altered adrenal function. Future studies should examine the physical stress of multiple exercise bouts to verify these findings and to explore the functional hormonal effects, such as immune and metabolic responses, during cancer treatment.

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer in men in the United States, accounting for approximately 20% of all new diagnoses and is the 3rd leading cause of cancer mortality [1]. Prostate tumors are commonly treated with surgery, radiation, and androgen

deprivation therapy (ADT), with the latter in particular being associated with a number of adverse effects including loss of muscle mass and increased fat mass [2], insulin resistance and frailty [3], and ultimately a reduced quality of life [4].

Over the past decade, exercise training during PCa treatment has been shown to be safe and effective in mitigating some side effects from PCa and ADT. Specifically, muscle strength, cardiorespiratory fitness, and physical function have consistently been shown to improve with exercise training [5, 6], while other traits (i.e. body composition) have demonstrated more variable responses [7-9]. As such, many organizations now recommend moderate intensity exercise as a complementary therapy to PCa treatment [10, 11]. However, there is limited data available on the endocrine response, specifically the stress hormones, following acute exercise in these patients. Given the importance of these hormones in health and exercise metabolism, it is important to understand the responses to ensure exercise is beneficial to all body systems and to better optimize exercise prescription.

Epinephrine (Epi), norepinephrine (NE), and cortisol are products of the adrenal gland and sympathetic nervous system activity with wide ranging effects that influence metabolism, body composition, and immune system function. Stress hormone release with exercise is intensity and duration-dependent in healthy individuals, with robust increases in circulating levels occurring when 30 minutes of exercise above 50-70% of maximal oxygen uptake is performed [12]. During PCa treatment, limited data on the stress hormone response to exercise exist. We are aware of only 1 study that showed cortisol levels were unchanged after both acute resistance exercise and resistance training while on ADT [13] and no reports of the exercise-induced response of Epi and NE. However, breast cancer (BCa) survivors have shown altered substrate utilization, reduced blood lactate levels, [14, 15] and attenuated Epi and cortisol responses after acute exercise relative to controls [16], which is a potential mechanism for differences in substrate utilization. While BCa is a different type of cancer, these tumors are also hormone-dependent and provide insight to the potential stress hormone response to acute exercise during PCa treatment.

While the stress hormone response to exercise is unclear in PCa patients, there is evidence of interactions between the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes in other populations [17], with chronic activation of the stress

systems leading to decreased production of sex and growth hormones [18]. Excess glucocorticoid production due to chronic stress leads to loss of lean mass and increases in visceral adiposity and insulin resistance, potentially exacerbating these symptoms already associated with ADT. Regarding stress in PCa patients, 30% of men are classified as clinically distressed prior to treatment [19] while 25% experience high anxiety post-diagnosis [20] and have greater psychological stress levels than non-cancer controls [21]. Chronic stress has immunosuppressive effects [22] and increases tumor growth [23], with NE specifically increasing prostate tumor migration [24]. Conversely, reducing cortisol levels enhanced natural killer cell activity [25]. Although the stress of cancer diagnosis and treatment is likely multi-factorial (e.g. psychological and physical), elevated anxiety and stress hormone release may promote a pro-oncogenic environment that has possible implications on long-term prognosis.

With a potentially elevated psychological stress levels, the addition of exercise may actually amplify activation of the stress hormone axes, possibly having negative consequences for PCa patients. Current exercise oncology guidelines are based on recommendations for older adults [10] and do not adequately consider the immuno-endocrine interaction during exercise [16], likely due to a lack of data. Given the key roles of these respective systems in maintaining health and physical function, a greater understanding of the stress hormone response of PCa patients during exercise is warranted to optimize exercise prescriptions while improving associated outcomes and quality of life. Moreover, the inclusion of ADT as a separate group allows for the effects of this specific treatment on the stress hormone response to exercise to be explored.

Therefore, the purpose of this study was to examine the effects of acute, moderate to vigorous intensity aerobic exercise on the stress hormone response in PCa patients with and without ADT compared with non-cancer controls to gain insight into the interactions of physical and psychological stress during PCa treatment. We hypothesized that PCa treatment, independent of ADT, would have higher baseline catecholamine and cortisol levels. We also hypothesized that the physical stress of interval exercise combined with psychological stress related to cancer treatment would produce significantly higher stress hormone levels post-exercise.

Methods

Participants

Men diagnosed with PCa on ADT [ADT; n=11, 67 (2yr)] and not on ADT [PCa; n=11, 67 (2y)] were recruited from local oncology practices and support groups in Melbourne, Australia along with non-cancer controls [n=8, 64 (3y)]. ADT and PCa patients had physician-diagnosed PCa, were sedentary (not regularly exercising except for walking, and no aerobic or strength training in previous 6 months) and were screened for acute or chronic conditions that would contraindicate participation in aerobic exercise. Men on ADT were treated with luteinizing releasing hormone agonists (91%) and anti-androgen receptor (9%) medications, and needed to be on treatment for at least 3 months prior to enrolling and throughout the study. Controls had no previous cancer diagnosis or treatment but met the same inclusion criteria otherwise. All participants received medical clearance from their general practitioner prior to participation.

Exclusion criteria included uncontrolled PCa, symptomatic cardiovascular disease, any conditions that caused severe pain with exertion, Type 1 diabetes, history of bone fractures, inability to engage safely in moderate exercise, or lack of medical clearance from their oncologist, urologist, general practitioner or specialist physician. The main exercise trial (visit 3) was controlled for time of day to minimize the effects of diurnal variations in hormone levels. The other tests were scheduled to minimize testing burden and aid in recruitment.

Familiarization (Visit 1)

Participants were informed of the study procedures and risks and all gave their written informed consent. This project was approved by the local ethics committees at Peter MacCallum Cancer Centre, Victoria University, and Western Health and was conducted in accordance with principles set out in the Declaration of Helsinki.

For the familiarization to the graded exercise test (GXT), participants were fitted with a mask to collect expired gases and to an electronically-braked cycle ergometer (Lode, Gronigen, Netherlands). Participants rested quietly until they were comfortable to proceed and then 3 to 4 submaximal stages (0 watts up to 60 or 80 watts) from the GXT were completed. All participants indicated they were comfortable with the GXT before leaving the laboratory.

Preliminary Testing (Visit 2)

Participants reported to the laboratory after having fasted for at least 2 hours, not exercised in the past 24 hours, and avoided caffeine and alcohol for 12 and 48 hours, respectively. These pre-assessment guidelines were confirmed verbally and were repeated at all

subsequent visits. The brief fatigue inventory (BFI) and functional assessment of cancer therapy-prostate (FACT-P) questionnaires were administered for fatigue and quality of life, respectively. Body composition was determined using dual-energy x-ray absorptiometry (Hologic, Waltham, MA, USA). Fat free mass was calculated as total mass – fat mass – bone mineral content. The scanner was calibrated daily and all scans were performed and analyzed by the same certified densitometry technician.

A GXT to determine peak oxygen consumption (VO_2peak) and to set the workload for the main trial was then performed. Participants rested quietly on the cycle ergometer for 3 minutes and then completed 1 minute stages beginning at 0 watts that increased by 20 watts until volitional exhaustion. Expired gases were sampled every 15 seconds using automated gas analyzers (Moxus Modular VO_2 System, AEI Technologies, Pittsburgh, PA, USA) and VO_2peak was determined as the average oxygen consumption across the last minute of the test. Gas analyzers were calibrated prior to each test using known gas concentrations (21.0% O_2 and 0.03% CO_2, 16.0% O_2 and 4.0% CO_2). Heart rate was assessed continuously via 12 lead electrocardiogram (GE Case Cardiosoft v6.6 ECG Diagnostic Systems, Palatine, IL, USA) and rate of perceived (RPE) exertion using the original Borg scale was assessed in the final 30 seconds of each stage. Following the GXT, participants completed a light cool down on the cycle ergometer and seated vital signs were monitored until heart rate and blood pressure approached resting values.

Trial Protocol (Visit 3 and 4)

Approximately one week later, participants returned to the laboratory for the main testing session (visit 3). All trials commenced between 0600 and 0900. After ~10 minutes of supine rest, a venous catheter was inserted into an antecubital forearm vein for repeat blood sampling and a resting blood sample was obtained. Participants completed an acute, intermittent exercise bout consisting of 10 intervals of 3 minutes of cycling at 60% of peak wattage from the GXT followed by 1.5 minutes of passive recovery without pedaling (45 minutes total time). Expired respiratory gases were sampled throughout the trial and the last minute of each exercise stage was used to determine oxygen consumption, respiratory exchange ratios, and the percentage of exercise relative to VO_2peak. Heart rate and RPE were obtained in the last 30 seconds of all stages. Additional blood samples were obtained immediately following exercise (0h) and at 2 hours (2h) post-exercise. During recovery, participants remained seated and consumed water *ad*

libitum. Twenty-four hours after the completion of visit 3, participants returned to the laboratory for an additional post-exercise (24h) blood sample (visit 4). Participants were asked to consume an identical meal prior to visits 3 and 4, in addition to the other pre-assessment guidelines.

Hormone Analysis

Serum and plasma blood tubes were obtained at each time point. Serum samples were allowed to clot at room temperature for 30 minutes first and all blood samples were kept on ice until the completion of the trial. Plasma and serum were isolated, aliquoted, and stored at -80°C. Prostate specific antigen levels (R & D Systems, Minneapolis, MN, USA) and total testosterone (Abnova, Taipei City, Taiwan) were determined at baseline only. Prostate specific antigen has a reported sensitivity of 0.030 ng/mL, an intra-assay CV of 3.0-7.2%, and an inter-assay CV of 4.8-6.8%. Testosterone had a reported sensitivity of 0.05 ng/mL, an intra-assay CV of 5.0-10.0%, and an inter-assay CV of 3.7-8.4%. Cortisol, NE and Epi were assessed at all time points (Abnova, Taipei City, Taiwan). Cortisol had a sensitivity of 1.5 ng/mL, an intra-assay CV of 6.2-9.4%, and an inter-assay CV of 8.6-15.0%. Epi had a limit of detection of 0.01 pg/mL, an intra-assay CV of 11.0-24.7%, and an inter-assay CV of 11.1-14.5%. NE had a limit of detection of 0.04 pg/mL, an intra-assay CV of 11.1-14.3%, and an inter-assay CV of 9.2-10.9%. All hormone analyses were performed in duplicate following manufacturer's instructions.

Hematology Analysis

Complete blood counts were determined using whole blood samples from each time point (Sysmex KX-21N, Kobe, Japan). All samples were analyzed in duplicate with a maximal white blood cell difference of 0.1 cells/μL and the values were averaged.

Statistical Analysis

A two-way (3x4) repeated measures ANOVA with Tukey HSD post-hoc was used to assess main effects of group, time and any interaction effects on the stress hormone response. One-way ANOVA was used to assess simple effect for any significant interactions and to compare participant characteristics. Data are presented as mean (SD) and the percent changes are expressed relative to baseline. All data were analyzed using SPSS v21 (Chicago, IL, USA). Figures were made in GraphPad Prism version 7 (La Jolla, CA, USA).

Results

Participants in this study were sedentary, borderline overweight, with men on ADT having significantly greater mass, % fat, and body mass index (all $p<0.05$, Table 1) with no

group difference for fat free mass. PCa patients were slightly more than 4 years post-diagnosis and those on ADT were approximately 3.5 years and had currently been on hormone therapy for 1.5 years at the time of study. Men on ADT had significantly lower total testosterone than PCa or controls ($p<0.001$) and had Gleeson scores and cancer stage scores at diagnosis that were higher than PCa (both $p<0.05$). Fatigue levels and co-morbidity index were similar across groups. There was a trend for reduced quality of life with ADT, as total FACT-P scores were lower than controls but this did not reach significance ($p=0.102$).

Absolute VO_2peak values were similar, with a trend for lower relative values with ADT ($p=0.060$, Table 2). All exercise trials were completed at 60% of VO_2peak wattage except for 2 individuals (n=1 PCa and n=1 ADT) that required reductions in resistance in the later stages to allow for completion. These stages showed little change in heart rate and no change in RPE compared to earlier in the trial. The response to the exercise trial was similar across groups, with an average heart rate and VO_2 that were slightly greater than 80% of the maximum values obtained during the GXT. Respiratory exchange ratios (RER) were significantly different overall ($p=0.040$), with the post hoc analysis indicating a trend for men with PCa to be greater than those on ADT and controls. The exercise session was viewed as "somewhat hard," based on an overall RPE rating of 12.6 (1.9).

For cortisol, there was no significant group x time interaction. Cortisol levels exhibited a biphasic response, significantly increasing by 36% ($p=0.012$) at 0h, declining to -24% of baseline at 2h ($p<0.001$), before returning to baseline levels at 24h (Figure 1). A main effect of group was observed, as cortisol levels with ADT were 32% lower than PCa ($p=0.006$) but were not different from controls.

There was no significant group x time interaction for NE. NE significantly increased by 385% at 0h ($p<0.001$) that remained elevated by 118% at 2h ($p<0.001$) but was similar to baseline by 24h (Figure 2). There were no differences between groups.

A significant group x time interaction was present for Epi ($p<0.001$, Figure 3). At 0h, controls demonstrated an 817% increase that was significantly greater than the changes seen with ADT (700%, $p=0.008$) and PCa (333%, $p=0.010$). No other time point was different from baseline or between groups. Due to subtle differences in baseline values and the small overall magnitude [ADT: 9.2 (10.9); PCa: 18.1 (16.1); controls: 21.1 (13.7)], the absolute change from baseline to 0h in Epi was also reported. Controls increased by 161.6 (72.8 pg/mL) but the

changes with ADT at 70.6 (63.8 pg/mL) and PCa at 69.6 (54.0 pg/mL) were significantly attenuated relative to controls (p=0.007).

There were no group differences for any leukocyte population at baseline (Supplemental Table 1). There were significant increases in lymphocyte and mixed cell counts at 0h compared to rest (both $p<0.01$) and at 0h and 2h compared to rest (all $p<0.01$) for neutrophils and total leukocytes.

Discussion

The aim of this preliminary study was to examine the stress hormone response after acute aerobic exercise in PCa patients with and without ADT compared to controls, which has previously not been reported. Contrary to our hypothesis, no baseline hormone differences were detected between groups, although cortisol levels were significantly reduced with ADT compared to PCa throughout the trial. All stress hormones significantly increased immediately after exercise before returning to baseline by 24h, supporting our hypothesis. However, the exercise-induced increase in Epi with PCa and ADT was attenuated, suggesting altered adrenal medulla function and partially supports observations from BCa survivors [16]. More importantly, there is no evidence of an exacerbated response to physical stress from a single bout of exercise during ADT, which would have had implications on several physiological systems and the use of physical activity to mitigate the side effects of PCa treatment.

A key finding is that PCa survivors with and without ADT do not have altered resting cortisol levels compared to controls. While previous work has indicated that PCa diagnosis and treatments increase anxiety and distress [19-21], this does not appear to affect circulating resting cortisol concentrations several years (~4 years) after diagnosis and completion of primary treatments. The lack of substantial differences in body composition and quality of life in the current study indirectly supports this finding. Individuals experiencing chronic stress experience smaller responses to physical or psychological challenges [26]. A flatter rise in cortisol indicates HPA dysfunction that is associated with higher cardiovascular morbidity [27], suppressed immune function, and lower cancer survival outcomes [28]. To explore this effect during PCa treatment, exercise-induced cortisol release exhibited a biphasic response, suggesting the HPA function is normal following a single bout of aerobic exercise. The 36% increase after aerobic exercise at 0h in the current study contrasts the lack of change (+3.8%) reported with resistance exercise [13] and aerobic exercise (-3.3%) [16], although intensity, exercise mode, and cancer type differences likely

influenced these comparisons. We found no evidence of hypercortisolism and hypogonadism working synergistically, as the cortisol response curve to acute exercise was similarly shaped and normal exercise-induced leukocytosis occurred. In fact, ADT significantly reduced cortisol levels across the trial compared with PCa alone but not controls. With ADT and complete androgen ablation, the crosstalk between the androgens and glucocorticoids may be disrupted. Previously, it has been shown that chronic stress can inhibit androgen production and there is evidence that this relationship may be bidirectional [18]. For example, abiraterone acetate used to treat castrate resistant PCa decreases testosterone and also cortisol [29]. In the current study, only luteinizing releasing hormone agonists and anti-androgen receptor medications were used to induce hypogonadism. We are not aware of any evidence directly showing that these medications influence circulating cortisol. However, numerous similarities between androgens and glucocorticoids and their respective receptors suggest that some forms of ADT influence the cortisol response [17].

Significant increases in catecholamine levels with acute aerobic exercise in PCa patients are a novel finding, as limited data exists for these markers during hormone-dependent cancer treatment [13, 16]. Stress hormones rise exponentially with exercise intensities beyond 50-70% of maximal oxygen uptake and durations of more than 30 minutes [12], which both occurred in the current study. For NE, PCa and ADT patients demonstrated nearly 4-fold increases immediately post-exercise and levels more than twice resting levels at 2h but overall were similar to controls, indicating a normal response. The heart rate response to exercise, which is primarily under sympathetic nervous system control and NE [30], was also similar across groups. Similar NE levels between groups at rest and with exercise has potential clinical application, as chronic NE administration increased mobility and migration of PCa tumor cell lines and metastatic progression in mice [24] and beta blocker treatment improves PCa prognosis [31]. Aerobic training decreases PCa progression in mice [32], possibly due to blunted exercise-induced NE release following training. However, stress hormone release during acute exercise is necessary to mobilize natural killer cells and reduce tumor volume [33]. These normal endocrine changes with exercise create an anti-tumor environment, provided the catecholamine increases are only transient.

Epi concentrations also significantly increased with exercise immediately post-exercise but returned to normal by 2h and 24h. In contrast to NE, the 0h rise in Epi was substantial less

pronounced with ADT and with PCa, with 700% and 333% increases respectively, compared to controls (817%). Moreover, the absolute changes clearly show that both cancer groups experienced increases that were approximately half that seen with controls. These data are consistent with previous work where Epi increased following exercise in controls but not in BCa patients [16]. Depending on the mode, repeated stress challenges may reduce the Epi response [for review see [34]]. For example, immobilization stress in rats failed to habituate even after 42 days [35] whereas repeated exercise exposure produced an attenuated Epi response [12]. As the blunted Epi response contrasts observations from NE and cortisol, this suggests that PCa treatment may alter adrenal medulla function with exercise. The adrenal medulla produces the majority of Epi in the body [34], whereas NE is derived primarily from spillover following sympathetic nervous system activity. It is possible that NE release from the adrenal medulla is also lower in PCa and ADT patients but is being masked by NE from sympathetic spillover. As measurements in this study were made from plasma, only total hormone concentrations were available and it was not possible to determine the source.

Stress hormones have a wide range of functions, including effects on metabolism. Obese men [36] and BCa patients on endocrine therapy following chemotherapy [15] have greater rates of fat oxidation during exercise at several different intensities compared to healthy individuals. As men on ADT present with greater % fat due to the hormone therapy, lower RER values were expected. Although ADT patients had RER values that were lower than PCa, substrate utilization was similar to controls. While greater fat utilization during exercise in obese individuals and BCa patients has been previously reported, this was not the case in this study, where all groups had high carbohydrate utilization (RER values were on average slightly less than 1.0). Even though statistically significant from the other groups, an RER value of 1.05 in PCa is not likely to be clinically relevant and would not drastically alter substrate utilization as all individuals were using primarily carbohydrate during exercise. Participants were at least 2h post-prandial and refrained from caffeine and alcohol intake, but diet was not strictly controlled and carbohydrate intake prior to or the morning of the trial for PCa patients could be influencing these results. As such, these findings need to be confirmed using more rigorous dietary controls.

Stress hormone concentrations returned to resting levels at 24h, signifying that exercise bouts of this fashion on consecutive days may be an option for patients. Leukocyte populations had returned to baseline levels after 24h (Supplemental Table 1) and similar immune cell

mobilization and cardiovascular outputs after exercise also support this. The modest difference in RER values discussed previously may be negligible with solely carbohydrate sources. We postulate that group differences in glycogen depletion after exercise would be minimal, as this has been shown to alter stress hormone levels during exercise [37].

Exercise oncology guidelines, based on recommendations for exercise in older adults, recommend 150 minutes of exercise per week, achieved through moderate intensity exercise on most (~5) days of the week or vigorous exercise 3 days per week [10, 11]. The classification of the exercise bout in the current study could be either moderate or vigorous. Participants rated the session as 'somewhat hard' on the Borg RPE scale, likely due to the rest intervals, whereas heart rate and VO_2 were both above 80% of the peak values obtained from the GXT and is consistent with vigorous exercise [15]. Our group has demonstrated previously that vigorous resistance exercise during ADT appears to be safe and may produce more favorable outcomes [8, 38] compared with trials using lower intensity [7]. Regarding safety, most exercise oncology studies have been conducted post-treatment except for ADT [7-9, 13]. For the current study, there were no adverse events during testing and there was only one patient (PCa group) who could not complete the exercise bout. Interestingly, this individual had recently (within 1-2 weeks) completed his radiation therapy. With n=1, this may be coincidental but supports the hypothesis that the exercise stress hormone response could be different in PCa patients undergoing active treatment. For instance, chemotherapy administered during BCa treatment was associated with higher musculoskeletal pain, weight issues, and nausea [39], which may increase the relative exercise intensity and the corresponding endocrine response.

This study has several strengths and limitations. It is the first to determine the stress hormones levels following aerobic exercise in PCa patients and provides novel information that the response to physical stress is relatively normal. We were also able to explore the specific effects of ADT. However, the small sample size requires that we designate these findings as preliminary. While our data appear promising that physical and cancer-related stress are not being compounded, these results are from a single exercise bout. Examining this response across multiple sessions may give better insight into the relationship with the stress hormone response and exercise training. Moreover, the patients were several years post-diagnosis and had been on ADT for more than a year. Newly diagnosed patients or those recently commencing ADT may respond differently, as coping strategies to the physical changes from treatment and

psychological burden may not have occurred. While most endocrine studies utilize continuous exercise, intervals were used to improve the likelihood of cancer patients being able to complete the trial by incorporating rest periods. While possibly affecting the response, this approach helped ensure that PCa and ADT patients achieved sufficient intensity and duration to stimulate sufficient stress hormone release. Lastly, despite attempts to match the participants on physical characteristics, a few differences in body composition exist that may have influenced the results.

In conclusion, this initial study using acute aerobic exercise to examine the stress hormone response during PCa treatment yielded several interesting findings, including lower overall cortisol levels with ADT and a blunted Epi response in both cancer groups. Here we show that 45 minutes of moderate to vigorous interval exercise stimulates a robust response but stress hormone levels returned to resting levels 24h, suggesting sufficient recovery from this single bout. Future directions should examine this response with micro- or meso-cycles to confirm these findings across multiple training bouts in recently diagnosed patients commencing treatment. Such approaches will allow for a more thorough analysis of the endocrine response to exercise during times of heightened psychological distress and to explore possible adrenal fatigue in PCa patients undergoing treatment. Furthermore, exploring the relationship between sex steroid ablation and low cortisol levels will allow for greater insight into the potential impact on the immune system; this is a pertinent question since both cortisol and sex steroids have been shown to impact the immune response. Collectively, this would permit improved exercise prescription that factors in additional physiological systems, leading to better use of exercise in managing the side effects of PCa treatment.

Perspectives

Exercise, particularly when performed at moderate to vigorous intensity, has demonstrated multiple benefits to cancer patients. Intense training has provided some of the most pronounced responses during ADT [5, 8, 38], but there are potential drawbacks that need be considered. Injury risk may increase and more subtle changes, such as immunosuppression or altered inflammatory responses are possible but have not yet been examined with appropriate designs. Studies that address these issues will allow for a greater understanding of the complex interactions between physiological systems that occur with exercise and cancer treatment. The ultimate goal is to provide individualized exercise prescription that takes into account a

multitude of factors (e.g. treatments, time since diagnosis, comorbidities) that are currently beyond our ability to control to optimize these complementary therapies and to enhance quality of life during cancer treatment.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67:7-30.

2. Galvao DA, Spry NA, Taaffe DR, Newton RU, Stanley J, Shannon T, Rowling C, Prince R. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int. 2008;102:44-47.

3. Cheung AS, Hoermann R, Dupuis P, Joon DL, Zajac JD, Grossmann M. Relationships between insulin resistance and frailty with body composition and testosterone in men undergoing androgen deprivation therapy for prostate cancer. Eur J Endocrinol. 2016;175:229-237.

4. Dacal K, Sereika SM, Greenspan SL. Quality of life in prostate cancer patients taking androgen deprivation therapy. J Am Geriatr Soc. 2006;54:85-90.

5. Hanson ED, Wagoner CW, Anderson T, Battaglini CL. The Independent Effects of Strength Training in Cancer Survivors: a Systematic Review. Curr Oncol Rep. 2016;18:31.

6. Gardner JR, Livingston PM, Fraser SF. Effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: a systematic review. J Clin Oncol. 2014;32:335-346.

7. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J Clin Oncol. 2010;28:340-347.

8. Hanson ED, Sheaff AK, Sood S, Ma L, Francis JD, Goldberg AP, Hurley BF. Strength training induces muscle hypertrophy and functional gains in black prostate cancer patients despite androgen deprivation therapy. J Gerontol A Biol Sci Med Sci. 2013;68:490-498.

9. Wall BA, Galvao DA, Fatehee N, Taaffe DR, Spry N, Joseph D, Hebert JJ, Newton RU. Exercise Improves V O2max and Body Composition in Androgen Deprivation Therapy-treated Prostate Cancer Patients. Med Sci Sports Exerc. 2017;49:1503-1510.

10. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, Irwin ML, Wolin KY, Segal RJ, Lucia A, Schneider CM, von Gruenigen VE, Schwartz AL, American College of Sports M. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42:1409-1426.

11. Hayes SC, Spence RR, Galvao DA, Newton RU. Australian Association for Exercise and Sport Science position stand: optimising cancer outcomes through exercise. J Sci Med Sport. 2009;12:428-434.

12. Brooks GA, Fahey TD, White TP, Baldwin KM. Neural-Endocrine Control of Metabolism. Exercise Physiology Human Bioenergetics and Its Applications. Mountain View, CA: Mayfield Publishing Group, 2000:165-196.

13. Galvao DA, Nosaka K, Taaffe DR, Peake J, Spry N, Suzuki K, Yamaya K, McGuigan MR, Kristjanson LJ, Newton RU. Endocrine and immune responses to resistance training in prostate cancer patients. Prostate Cancer Prostatic Dis. 2008;11:160-165.

14. Evans ES, Battaglini CL, Groff DG, Hackney AC. Aerobic exercise intensity in breast cancer patients: a preliminary investigation. Integr Cancer Ther. 2009;8:139-147.

15. Tosti KP, Hackney AC, Battaglini CL, Evans ES, Groff D. Exercise in patients with breast cancer and healthy controls: energy substrate oxidation and blood lactate responses. Integr Cancer Ther. 2011;10:6-15.

16. Evans ES, Hackney AC, Pebole MM, McMurray RG, Muss HB, Deal AM, Battaglini CL. Adrenal Hormone and Metabolic Biomarker Responses to 30 min of Intermittent Cycling Exercise in Breast Cancer Survivors. Int J Sports Med. 2016;37:921-929.

452 17. Claessens F, Joniau S, Helsen C. Comparing the rules of engagement of androgen and
453 glucocorticoid receptors. Cell Mol Life Sci. 2017;74:2217-2228.

454 18. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and
455 stress. J Psychosom Res. 2002;53:865-871.

456 19. Carlson LE, Angen M, Cullum J, Goodey E, Koopmans J, Lamont L, MacRae JH, Martin
457 M, Pelletier G, Robinson J, Simpson JS, Speca M, Tillotson L, Bultz BD. High levels of
458 untreated distress and fatigue in cancer patients. Br J Cancer. 2004;90:2297-2304.

459 20. Korfage IJ, Essink-Bot ML, Janssens AC, Schroder FH, de Koning HJ. Anxiety and
460 depression after prostate cancer diagnosis and treatment: 5-year follow-up. Br J Cancer.
461 2006;94:1093-1098.

462 21. Yermal SJ, Witek-Janusek L, Peterson J, Mathews HL. Perioperative pain, psychological
463 distress, and immune function in men undergoing prostatectomy for cancer of the prostate. Biol
464 Res Nurs. 2010;11:351-362.

465 22. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of
466 glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol.
467 2011;335:2-13.

468 23. Thaker PH, Han LY, Kamat AA, Arevalo JM, Takahashi R, Lu C, Jennings NB, Armaiz-
469 Pena G, Bankson JA, Ravoori M, Merritt WM, Lin YG, Mangala LS, Kim TJ, Coleman RL,
470 Landen CN, Li Y, Felix E, Sanguino AM, Newman RA, Lloyd M, Gershenson DM, Kundra V,
471 Lopez-Berestein G, Lutgendorf SK, Cole SW, Sood AK. Chronic stress promotes tumor growth
472 and angiogenesis in a mouse model of ovarian carcinoma. Nat Med. 2006;12:939-944.

473 24. Barbieri A, Bimonte S, Palma G, Luciano A, Rea D, Giudice A, Scognamiglio G, La
474 Mantia E, Franco R, Perdona S, De Cobelli O, Ferro M, Zappavigna S, Stiuso P, Caraglia M,
475 Arra C. The stress hormone norepinephrine increases migration of prostate cancer cells in vitro
476 and in vivo. Int J Oncol. 2015;47:527-534.

477 25. Raja Gabaglia C, Diaz de Durana Y, Graham FL, Gauldie J, Sercarz EE, Braciak TA.
478 Attenuation of the glucocorticoid response during Ad5IL-12 adenovirus vector treatment

enhances natural killer cell-mediated killing of MHC class I-negative LNCaP prostate tumors. Cancer Res. 2007;67:2290-2297.

26. Wessa M, Rohleder N, Kirschbaum C, Flor H. Altered cortisol awakening response in posttraumatic stress disorder. Psychoneuroendocrinology. 2006;31:209-215.

27. Matthews K, Schwartz J, Cohen S, Seeman T. Diurnal cortisol decline is related to coronary calcification: CARDIA study. Psychosom Med. 2006;68:657-661.

28. Sephton SE, Sapolsky RM, Kraemer HC, Spiegel D. Diurnal cortisol rhythm as a predictor of breast cancer survival. J Natl Cancer Inst. 2000;92:994-1000.

29. Narayanan S, Srinivas S, Feldman D. Androgen-glucocorticoid interactions in the era of novel prostate cancer therapy. Nat Rev Urol. 2016;13:47-60.

30. Terjung R. Endocrine response to exercise. Exerc Sport Sci Rev. 1979;7:153-180.

31. Krizanova O, Babula P, Pacak K. Stress, catecholaminergic system and cancer. Stress. 2016;19:419-428.

32. Esser KA, Harpole CE, Prins GS, Diamond AM. Physical activity reduces prostate carcinogenesis in a transgenic model. Prostate. 2009;69:1372-1377.

33. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, Johannesen HH, Becker JC, Pedersen KS, Dethlefsen C, Nielsen J, Gehl J, Pedersen BK, Thor Straten P, Hojman P. Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. Cell Metab. 2016;23:554-562.

34. Wong DL, Tai TC, Wong-Faull DC, Claycomb R, Meloni EG, Myers KM, Carlezon WA, Jr., Kvetnansky R. Epinephrine: a short- and long-term regulator of stress and development of illness : a potential new role for epinephrine in stress. Cell Mol Neurobiol. 2012;32:737-748.

35. Kvetnansky R, Nankova BB, Rusnak M, Micutkova L, Kubovcakova L, Dronjak SK, Krizanova O, Sabban EL. Differential gene expression of tyrosine hydroxylase in rats exposed long-term to various stressors. In: Nagatsu T, Nabeshima T, McCarty R, Goldstein DS, eds.

Catecholamine Research Advances in Behavioral Biology. Boston, MA: Springer, 2002:317-320.

36. Goodpaster BH, Wolfe RR, Kelley DE. Effects of obesity on substrate utilization during exercise. Obes Res. 2002;10:575-584.

37. Podolin DA, Munger PA, Mazzeo RS. Plasma catecholamine and lactate response during graded exercise with varied glycogen conditions. J Appl Physiol (1985). 1991;71:1427-1433.

38. Hanson ED, Nelson AR, West DW, Violet JA, O'Keefe L, Phillips SM, Hayes A. Attenuation of Resting but Not Load-Mediated Protein Synthesis in Prostate Cancer Patients on Androgen Deprivation. J Clin Endocrinol Metab. 2017;102:1076-1083.

39. Ganz PA, Kwan L, Stanton AL, Bower JE, Belin TR. Physical and psychosocial recovery in the year after primary treatment of breast cancer. J Clin Oncol. 2011;29:1101-1109.

Figure Captions

Figure 1. Cortisol levels significantly increased in response to acute, intermittent aerobic exercise during prostate cancer treatment. ADT was significantly less than PCa throughout but was not different than controls (CON). Data are represented mean (SD). Time points with different letters are significantly different from each other ($p<0.05$). † Indicates group difference for ADT vs. PCa ($p=0.006$).

Figure 2. Norepinephrine (NE) levels at rest and in response to acute, intermittent aerobic exercise during prostate cancer treatment. No group differences were observed. Data are represented mean (SD). Time points with different letters are significantly different from each other ($p<0.05$).

Figure 3. Changes in epinephrine (EPI) levels in response to acute, intermittent aerobic exercise are attenuated during prostate cancer treatment compared to controls (CON). Data are represented mean (SD). Time points with different letters are significantly different from each other ($p<0.05$).

# Indicates CON was significantly different than PCa and ADT group at the specific time point ($p<0.001$).

Table 1. Participant characteristics.

	CON (n=8)	PCa (n=11)	ADT (n=11)	P value
Height (m)	172.8 (4.1)	164.9 (33.3)	173.1 (8.1)	0.602
Mass (kg)	74.7 (6.7)	79.7 (9.2)	91.9 (19.8) [a]	0.030
Body mass index	25.0 (1.9)	26.4 (3.0)	30.6 (5.1) [a,b]	0.007
% Fat	20.4 (3.2)	25.0 (4.1)	29.9 (6.7) [a,b]	0.002
Fat free mass (kg)	55.4 (5.0)	56.2 (6.2)	59.6 (8.9)	0.390
Total testosterone (ng/dL)	669.2 (231.2)	640.7 (354.2)	46.3 (23.5) [a,b]	<0.001
Prostate specific antigen (ng/mL)	1.9 (1.2)	1.6 (2.5)	9.3 (26.8)	0.438
Brief fatigue index	1.5 (1.9)	2.3 (2.0)	1.9 (2.2)	0.831
FACT-P	135 (10)	126 (16)	121 (12)	0.102
Prostate cancer stage	-	1.6 (0.7)	2.6 (1.1)	0.021
Gleeson score	-	6.6 (0.5)	7.6 (1.0)	0.009
Days since diagnosis	-	1497 (1137)	1244 (1370)	0.642
Prostatectomy (%)	-	4 (36%)	4 (36%)	-
Radiation therapy (%)	-	7 (64%)	6 (55%)	-
ADT length (days)	-	-	579 (383)	-
Co-morbidity sum	1.4 (1.1)	1.7 (1.0)	1.5 (1.1)	0.794

Mean (SD). Co-morbidity sum is the total number of the following conditions: hypertension, hypercholesterolemia, Type II diabetes, smoker/former smoker, and regular alcohol consumption. FACT-P = Functional assessment of cancer therapy-prostate.

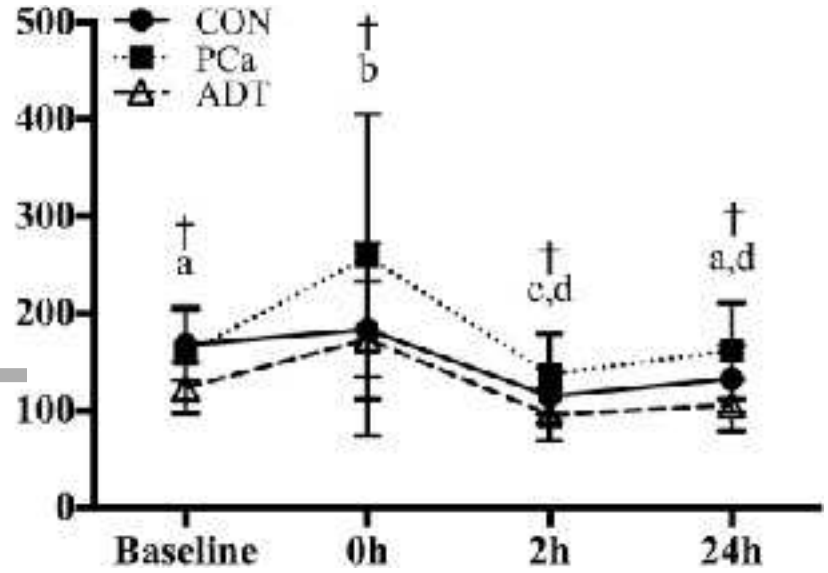
[a] Significantly different from CON ($P<0.05$); [b] Significantly different from PCa ($P<0.05$).

Table 2. The average exercise (60% of workload maximum from GXT) and recovery physiological responses during 10 bouts of intermittent exercise.

	CON	PCa	ADT	P value
VO_2peak (L/min)	2.4 (0.6)	2.0 (0.5)	2.1 (0.6)	0.316
VO_2peak (mL/kg/min)	32.4 (8.6)	25.1 (5.8)	23.9 (8.4)	0.060
Trial workload (watts)	123 (26)	96 (31)	107 (43)	0.285
Average Exercise HR (bpm)	130 (10)	124 (16)	131 (20)	0.598
Average Exercise % HRmax	82.1 (9.5)	82.1 (9.5)	85.1 (15.1)	0.877
Average Recovery HR (bpm)	101 (15)	101 (15)	104 (18)	0.830
Average Exercise VO_2 (ml/kg/min)	24.7 (4.5)	19.9 (3.8)	20.7 (5.6)	0.085
Average % VO_2peak	77.6 (6.4)	80.5 (9.0)	84.8 (8.1)	0.188
Average Recovery VO_2 (ml/kg/min)	12.5 (1.8)	11.1 (1.9)	10.8 (1.6)	0.137
Average Exercise RPE	13.0 (2.2)	12.1 (1.3)	12.2 (2.3)	0.464
Average Exercise RER	0.98 (0.04)	1.05 (0.08)	0.98 (0.06)	0.040[†]
Post-Ex PV shift (%)	-13.8 (4.1)	-12.7 (5.0)	-13.7 (4.6)	0.825

Mean (SD). VO_2peak = peak oxygen consumption; HR = heart rate; RPE = rate of perceived exertion; RER = respiratory exchange ratio; PV = plasma volume

[†] Trend for PCa to be higher than CON and ADT (P=0.070 and P=0.082, respectively)



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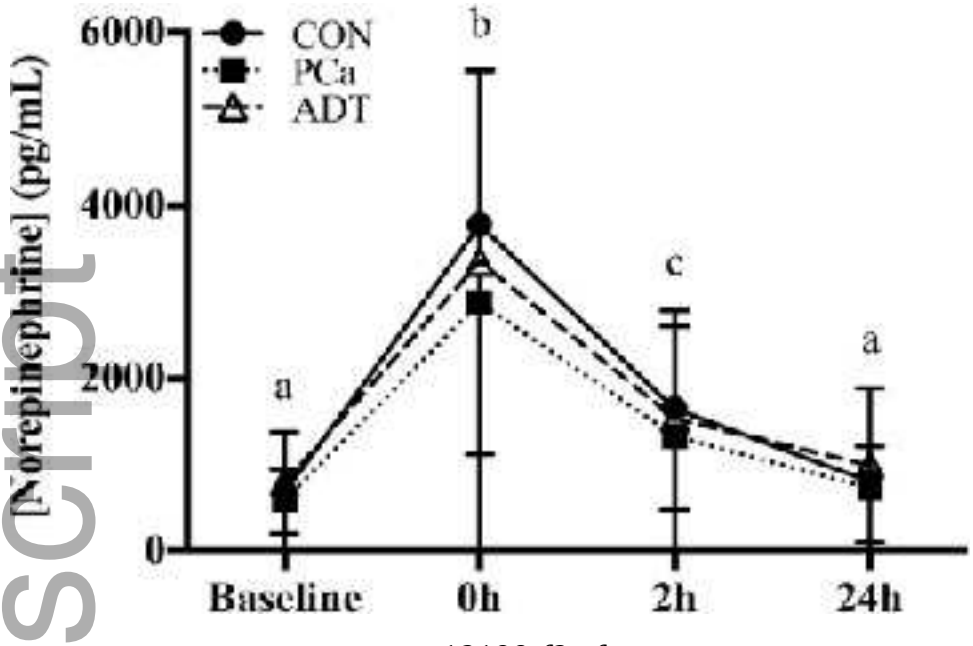

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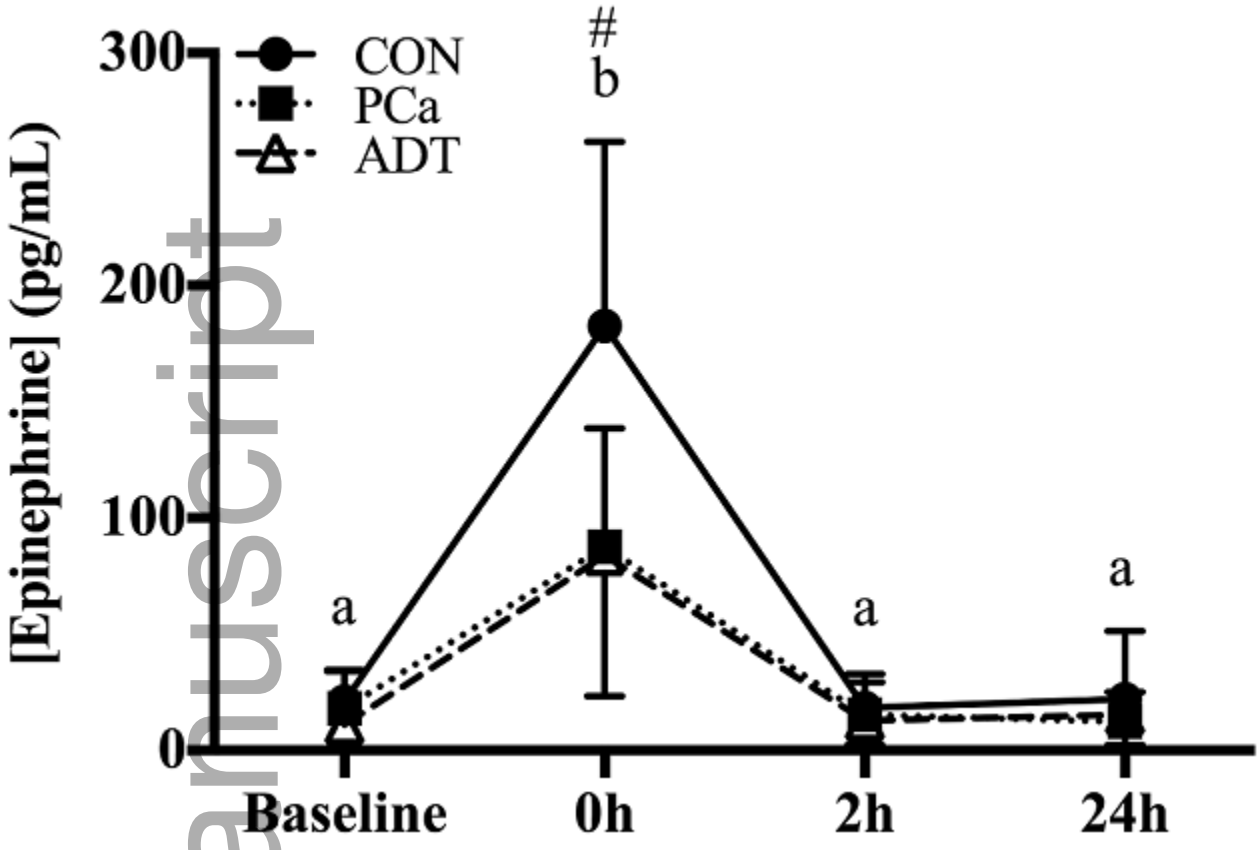

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