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1 Altered Stress Hormone Response Following Acute Exercise During Prostate Cancer Treatment

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24 **Key Words:** stress response, acute exercise, cortisol, androgen deprivation therapy,

25 catecholamines

26 **Abstract**

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

45 **Introduction**

46 Prostate cancer (PCa) is the most commonly diagnosed cancer in men in the United States,
47 accounting for approximately 20% of all new diagnoses and is the 3rd leading cause of cancer
48 mortality ¹. Prostate tumors are commonly treated with surgery, radiation, and androgen
49 deprivation therapy (ADT), with the latter in particular being associated with a number of adverse
50 effects including loss of muscle mass and increased fat mass ², insulin resistance and frailty ³, and
51 ultimately a reduced quality of life ⁴.

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

62 Epinephrine (Epi), norepinephrine (NE), and cortisol are products of the adrenal gland and
63 sympathetic nervous system activity with wide ranging effects that influence metabolism, body
64 composition, and immune system function. Stress hormone release with exercise is intensity and
65 duration-dependent in healthy individuals, with robust increases in circulating levels occurring
66 when 30 minutes of exercise above 50-70% of maximal oxygen uptake is performed ¹². During
67 PCa treatment, limited data on the stress hormone response to exercise exist. We are aware of only

68 1 study that showed cortisol levels were unchanged after both acute resistance exercise and
69 resistance training while on ADT ¹³ and no reports of the exercise-induced response of Epi and
70 NE. However, breast cancer (BCa) survivors have shown altered substrate utilization, reduced
71 blood lactate levels, ^{14, 15} and attenuated Epi and cortisol responses after acute exercise relative to
72 controls ¹⁶, which is a potential mechanism for differences in substrate utilization. While BCa is a
73 different type of cancer, these tumors are also hormone-dependent and provide insight to the
74 potential stress hormone response to acute exercise during PCa treatment.

75 While the stress hormone response to exercise is unclear in PCa patients, there is evidence
76 of interactions between the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-
77 gonadal (HPG) axes in other populations ¹⁷, with chronic activation of the stress systems leading
78 to decreased production of sex and growth hormones ¹⁸. Excess glucocorticoid production due to
79 chronic stress leads to loss of lean mass and increases in visceral adiposity and insulin resistance,
80 potentially exacerbating these symptoms already associated with ADT. Regarding stress in PCa
81 patients, 30% of men are classified as clinically distressed prior to treatment ¹⁹ while 25%
82 experience high anxiety post-diagnosis ²⁰ and have greater psychological stress levels than non-
83 cancer controls ²¹. Chronic stress has immunosuppressive effects ²² and increases tumor growth ²³,
84 with NE specifically increasing prostate tumor migration ²⁴. Conversely, reducing cortisol levels
85 enhanced natural killer cell activity ²⁵. Although the stress of cancer diagnosis and treatment is
86 likely multi-factorial (e.g. psychological and physical), elevated anxiety and stress hormone
87 release may promote a pro-oncogenic environment that has possible implications on long-term
88 prognosis.

89 With a potentially elevated psychological stress levels, the addition of exercise may
90 actually amplify activation of the stress hormone axes, possibly having negative consequences for

91 PCa patients. Current exercise oncology guidelines are based on recommendations for older adults
92 ¹⁰ and do not adequately consider the immuno-endocrine interaction during exercise ¹⁶, likely due
93 to a lack of data. Given the key roles of these respective systems in maintaining health and physical
94 function, a greater understanding of the stress hormone response of PCa patients during exercise
95 is warranted to optimize exercise prescriptions while improving associated outcomes and quality
96 of life. Moreover, the inclusion of ADT as a separate group allows for the effects of this specific
97 treatment on the stress hormone response to exercise to be explored.

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

105 **Methods**

106 *Participants*

107 Men diagnosed with PCa on ADT [ADT; n=11, 67 (2yr)] and not on ADT [PCa; n=11, 67
108 (2y)] were recruited from local oncology practices and support groups in Melbourne, Australia
109 along with non-cancer controls [n=8, 64 (3y)]. ADT and PCa patients had physician-diagnosed
110 PCa, were sedentary (not regularly exercising except for walking, and no aerobic or strength
111 training in previous 6 months) and were screened for acute or chronic conditions that would
112 contraindicate participation in aerobic exercise. Men on ADT were treated with luteinizing
113 releasing hormone agonists (91%) and anti-androgen receptor (9%) medications, and needed to be
114 on treatment for at least 3 months prior to enrolling and throughout the study. Controls had no
115 previous cancer diagnosis or treatment but met the same inclusion criteria otherwise. All
116 participants received medical clearance from their general practitioner prior to participation.

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

123 *Familiarization (Visit 1)*

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

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

133 *Preliminary Testing (Visit 2)*

134 Participants reported to the laboratory after having fasted for at least 2 hours, not exercised
135 in the past 24 hours, and avoided caffeine and alcohol for 12 and 48 hours, respectively. These
136 pre-assessment guidelines were confirmed verbally and were repeated at all subsequent visits. The
137 brief fatigue inventory (BFI) and functional assessment of cancer therapy-prostate (FACT-P)
138 questionnaires were administered for fatigue and quality of life, respectively. Body composition
139 was determined using dual-energy x-ray absorptiometry (Hologic, Waltham, MA, USA). Fat free
140 mass was calculated as total mass – fat mass – bone mineral content. The scanner was calibrated
141 daily and all scans were performed and analyzed by the same certified densitometry technician.

142 A GXT to determine peak oxygen consumption (VO_{2peak}) and to set the workload for the
143 main trial was then performed. Participants rested quietly on the cycle ergometer for 3 minutes
144 and then completed 1 minute stages beginning at 0 watts that increased by 20 watts until volitional
145 exhaustion. Expired gases were sampled every 15 seconds using automated gas analyzers (Moxus
146 Modular VO_2 System, AEI Technologies, Pittsburgh, PA, USA) and VO_{2peak} was determined as
147 the average oxygen consumption across the last minute of the test. Gas analyzers were calibrated
148 prior to each test using known gas concentrations (21.0% O_2 and 0.03% CO_2 , 16.0% O_2 and 4.0%
149 CO_2). Heart rate was assessed continuously via 12 lead electrocardiogram (GE Case CardioSoft
150 v6.6 ECG Diagnostic Systems, Palatine, IL, USA) and rate of perceived (RPE) exertion using the

151 original Borg scale was assessed in the final 30 seconds of each stage. Following the GXT,
152 participants completed a light cool down on the cycle ergometer and seated vital signs were
153 monitored until heart rate and blood pressure approached resting values.

154 *Trial Protocol (Visit 3 and 4)*

155 Approximately one week later, participants returned to the laboratory for the main testing
156 session (visit 3). All trials commenced between 0600 and 0900. After ~10 minutes of supine rest,
157 a venous catheter was inserted into an antecubital forearm vein for repeat blood sampling and a
158 resting blood sample was obtained. Participants completed an acute, intermittent exercise bout
159 consisting of 10 intervals of 3 minutes of cycling at 60% of peak wattage from the GXT followed
160 by 1.5 minutes of passive recovery without pedaling (45 minutes total time). Expired respiratory
161 gases were sampled throughout the trial and the last minute of each exercise stage was used to
162 determine oxygen consumption, respiratory exchange ratios, and the percentage of exercise
163 relative to VO_{2peak} . Heart rate and RPE were obtained in the last 30 seconds of all stages.
164 Additional blood samples were obtained immediately following exercise (0h) and at 2 hours (2h)
165 post-exercise. During recovery, participants remained seated and consumed water *ad libitum*.
166 Twenty-four hours after the completion of visit 3, participants returned to the laboratory for an
167 additional post-exercise (24h) blood sample (visit 4). Participants were asked to consume an
168 identical meal prior to visits 3 and 4, in addition to the other pre-assessment guidelines.

169 *Hormone Analysis*

170 Serum and plasma blood tubes were obtained at each time point. Serum samples were
171 allowed to clot at room temperature for 30 minutes first and all blood samples were kept on ice
172 until the completion of the trial. Plasma and serum were isolated, aliquoted, and stored at -80°C.
173 Prostate specific antigen levels (R & D Systems, Minneapolis, MN, USA) and total testosterone

174 (Abnova, Taipei City, Taiwan) were determined at baseline only. Prostate specific antigen has a
175 reported sensitivity of 0.030 ng/mL, an intra-assay CV of 3.0-7.2%, and an inter-assay CV of 4.8-
176 6.8%. Testosterone had a reported sensitivity of 0.05 ng/mL, an intra-assay CV of 5.0-10.0%, and
177 an inter-assay CV of 3.7-8.4%. Cortisol, NE and Epi were assessed at all time points (Abnova,
178 Taipei City, Taiwan). Cortisol had a sensitivity of 1.5 ng/mL, an intra-assay CV of 6.2-9.4%, and
179 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
180 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
181 intra-assay CV of 11.1-14.3%, and an inter-assay CV of 9.2-10.9%. All hormone analyses were
182 performed in duplicate following manufacturer's instructions.

183 *Hematology Analysis*

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

187 *Statistical Analysis*

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

194 **Results**

195 Participants in this study were sedentary, borderline overweight, with men on ADT having
196 significantly greater mass, % fat, and body mass index (all $p < 0.05$, Table 1) with no group
197 difference for fat free mass. PCa patients were slightly more than 4 years post-diagnosis and those
198 on ADT were approximately 3.5 years and had currently been on hormone therapy for 1.5 years at
199 the time of study. Men on ADT had significantly lower total testosterone than PCa or controls
200 ($p < 0.001$) and had Gleason scores and cancer stage scores at diagnosis that were higher than PCa
201 (both $p < 0.05$). Fatigue levels and co-morbidity index were similar across groups. There was a trend
202 for reduced quality of life with ADT, as total FACT-P scores were lower than controls but this did
203 not reach significance ($p = 0.102$).

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

214 For cortisol, there was no significant group x time interaction. Cortisol levels exhibited a
215 biphasic response, significantly increasing by 36% ($p = 0.012$) at 0h, declining to -24% of baseline
216 at 2h ($p < 0.001$), before returning to baseline levels at 24h (Figure 1). A main effect of group was

217 observed, as cortisol levels with ADT were 32% lower than PCa ($p=0.006$) but were not different
218 from controls.

219 There was no significant group x time interaction for NE. NE significantly increased by
220 385% at 0h ($p<0.001$) that remained elevated by 118% at 2h ($p<0.001$) but was similar to baseline
221 by 24h (Figure 2). There were no differences between groups.

222 A significant group x time interaction was present for Epi ($p<0.001$, Figure 3). At 0h,
223 controls demonstrated an 817% increase that was significantly greater than the changes seen with
224 ADT (700%, $p=0.008$) and PCa (333%, $p=0.010$). No other time point was different from baseline
225 or between groups. Due to subtle differences in baseline values and the small overall magnitude
226 [ADT: 9.2 (10.9); PCa: 18.1 (16.1); controls: 21.1 (13.7)], the absolute change from baseline to 0h
227 in Epi was also reported. Controls increased by 161.6 (72.8 pg/mL) but the changes with ADT at
228 70.6 (63.8 pg/mL) and PCa at 69.6 (54.0 pg/mL) were significantly attenuated relative to controls
229 ($p=0.007$).

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

234 **Discussion**

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

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

257 in the current study contrasts the lack of change (+3.8%) reported with resistance exercise ¹³ and
258 aerobic exercise (-3.3%) ¹⁶, although intensity, exercise mode, and cancer type differences likely
259 influenced these comparisons. We found no evidence of hypercortisolism and hypogonadism
260 working synergistically, as the cortisol response curve to acute exercise was similarly shaped and
261 normal exercise-induced leukocytosis occurred. In fact, ADT significantly reduced cortisol levels
262 across the trial compared with PCa alone but not controls. With ADT and complete androgen
263 ablation, the crosstalk between the androgens and glucocorticoids may be disrupted. Previously, it
264 has been shown that chronic stress can inhibit androgen production and there is evidence that this
265 relationship may be bidirectional ¹⁸. For example, abiraterone acetate used to treat castrate resistant
266 PCa decreases testosterone and also cortisol ²⁹. In the current study, only luteinizing releasing
267 hormone agonists and anti-androgen receptor medications were used to induce hypogonadism. We
268 are not aware of any evidence directly showing that these medications influence circulating
269 cortisol. However, numerous similarities between androgens and glucocorticoids and their
270 respective receptors suggest that some forms of ADT influence the cortisol response ¹⁷.

271 Significant increases in catecholamine levels with acute aerobic exercise in PCa patients
272 are a novel finding, as limited data exists for these markers during hormone-dependent cancer
273 treatment ^{13, 16}. Stress hormones rise exponentially with exercise intensities beyond 50-70% of
274 maximal oxygen uptake and durations of more than 30 minutes ¹², which both occurred in the
275 current study. For NE, PCa and ADT patients demonstrated nearly 4-fold increases immediately
276 post-exercise and levels more than twice resting levels at 2h but overall were similar to controls,
277 indicating a normal response. The heart rate response to exercise, which is primarily under
278 sympathetic nervous system control and NE ³⁰, was also similar across groups. Similar NE levels
279 between groups at rest and with exercise has potential clinical application, as chronic NE

280 administration increased mobility and migration of PCa tumor cell lines and metastatic progression
281 in mice ²⁴ and beta blocker treatment improves PCa prognosis ³¹. Aerobic training decreases PCa
282 progression in mice ³², possibly due to blunted exercise-induced NE release following training.
283 However, stress hormone release during acute exercise is necessary to mobilize natural killer cells
284 and reduce tumor volume ³³. These normal endocrine changes with exercise create an anti-tumor
285 environment, provided the catecholamine increases are only transient.

286 Epi concentrations also significantly increased with exercise immediately post-exercise but
287 returned to normal by 2h and 24h. In contrast to NE, the 0h rise in Epi was substantial less
288 pronounced with ADT and with PCa, with 700% and 333% increases respectively, compared to
289 controls (817%). Moreover, the absolute changes clearly show that both cancer groups experienced
290 increases that were approximately half that seen with controls. These data are consistent with
291 previous work where Epi increased following exercise in controls but not in BCa patients ¹⁶.
292 Depending on the mode, repeated stress challenges may reduce the Epi response [for review see
293 ³⁴]. For example, immobilization stress in rats failed to habituate even after 42 days ³⁵ whereas
294 repeated exercise exposure produced an attenuated Epi response ¹². As the blunted Epi response
295 contrasts observations from NE and cortisol, this suggests that PCa treatment may alter adrenal
296 medulla function with exercise. The adrenal medulla produces the majority of Epi in the body ³⁴,
297 whereas NE is derived primarily from spillover following sympathetic nervous system activity. It
298 is possible that NE release from the adrenal medulla is also lower in PCa and ADT patients but is
299 being masked by NE from sympathetic spillover. As measurements in this study were made from
300 plasma, only total hormone concentrations were available and it was not possible to determine the
301 source.

302 Stress hormones have a wide range of functions, including effects on metabolism. Obese
303 men³⁶ and BCa patients on endocrine therapy following chemotherapy¹⁵ have greater rates of fat
304 oxidation during exercise at several different intensities compared to healthy individuals. As men
305 on ADT present with greater % fat due to the hormone therapy, lower RER values were expected.
306 Although ADT patients had RER values that were lower than PCa, substrate utilization was similar
307 to controls. While greater fat utilization during exercise in obese individuals and BCa patients has
308 been previously reported, this was not the case in this study, where all groups had high
309 carbohydrate utilization (RER values were on average slightly less than 1.0). Even though
310 statistically significant from the other groups, an RER value of 1.05 in PCa is not likely to be
311 clinically relevant and would not drastically alter substrate utilization as all individuals were using
312 primarily carbohydrate during exercise. Participants were at least 2h post-prandial and refrained
313 from caffeine and alcohol intake, but diet was not strictly controlled and carbohydrate intake prior
314 to or the morning of the trial for PCa patients could be influencing these results. As such, these
315 findings need to be confirmed using more rigorous dietary controls.

316 Stress hormone concentrations returned to resting levels at 24h, signifying that exercise
317 bouts of this fashion on consecutive days may be an option for patients. Leukocyte populations
318 had returned to baseline levels after 24h (Supplemental Table 1) and similar immune cell
319 mobilization and cardiovascular outputs after exercise also support this. The modest difference in
320 RER values discussed previously may be negligible with solely carbohydrate sources. We
321 postulate that group differences in glycogen depletion after exercise would be minimal, as this has
322 been shown to alter stress hormone levels during exercise³⁷.

323 Exercise oncology guidelines, based on recommendations for exercise in older adults,
324 recommend 150 minutes of exercise per week, achieved through moderate intensity exercise on

325 most (~5) days of the week or vigorous exercise 3 days per week ^{10, 11}. The classification of the
326 exercise bout in the current study could be either moderate or vigorous. Participants rated the
327 session as ‘somewhat hard’ on the Borg RPE scale, likely due to the rest intervals, whereas heart
328 rate and VO₂ were both above 80% of the peak values obtained from the GXT and is consistent
329 with vigorous exercise ¹⁵. Our group has demonstrated previously that vigorous resistance exercise
330 during ADT appears to be safe and may produce more favorable outcomes ^{8, 38} compared with
331 trials using lower intensity ⁷. Regarding safety, most exercise oncology studies have been
332 conducted post-treatment except for ADT ^{7-9, 13}. For the current study, there were no adverse events
333 during testing and there was only one patient (PCa group) who could not complete the exercise
334 bout. Interestingly, this individual had recently (within 1-2 weeks) completed his radiation therapy.
335 With n=1, this may be coincidental but supports the hypothesis that the exercise stress hormone
336 response could be different in PCa patients undergoing active treatment. For instance,
337 chemotherapy administered during BCa treatment was associated with higher musculoskeletal
338 pain, weight issues, and nausea ³⁹, which may increase the relative exercise intensity and the
339 corresponding endocrine response.

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

348 year. Newly diagnosed patients or those recently commencing ADT may respond differently, as
349 coping strategies to the physical changes from treatment and psychological burden may not have
350 occurred. While most endocrine studies utilize continuous exercise, intervals were used to improve
351 the likelihood of cancer patients being able to complete the trial by incorporating rest periods.
352 While possibly affecting the response, this approach helped ensure that PCa and ADT patients
353 achieved sufficient intensity and duration to stimulate sufficient stress hormone release. Lastly,
354 despite attempts to match the participants on physical characteristics, a few differences in body
355 composition exist that may have influenced the results.

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

371

372 **Perspectives**

373 Exercise, particularly when performed at moderate to vigorous intensity, has demonstrated
374 multiple benefits to cancer patients. Intense training has provided some of the most pronounced
375 responses during ADT ^{5, 8, 38}, but there are potential drawbacks that need be considered. Injury risk
376 may increase and more subtle changes, such as immunosuppression or altered inflammatory
377 responses are possible but have not yet been examined with appropriate designs. Studies that
378 address these issues will allow for a greater understanding of the complex interactions between
379 physiological systems that occur with exercise and cancer treatment. The ultimate goal is to
380 provide individualized exercise prescription that takes into account a multitude of factors (e.g.
381 treatments, time since diagnosis, comorbidities) that are currently beyond our ability to control to
382 optimize these complementary therapies and to enhance quality of life during cancer treatment.

383

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- 498

499 **Figure Captions**

500

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

506

507

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

511

512

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

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