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Effect of Aerobic Fitness on Cortisol Response and Hypothalamic–Pituitary–Adrenal Axis Reactivity at Different Aerobic Exercise Intensities

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Abstract
Cortisol is a hormone typically associated with the body's reaction to a stressor. As exercise intensity increases, the hypothalamic–pituitary–adrenal axis (HPA-axis) reacts to the negative net energy demand by releasing cortisol to increase the availability of energy substrates to supply the working muscles and organs. This evidence-based review assesses multiple positive and negative feedback mechanisms associated with the HPA-axis to explain its reactivity to aerobic exercise at different intensities where a marked increase in salivary cortisol is observed at exercise intensities above 60% of one's heart rate reserve. The review also explains different mechanisms as to how an increase in maximal aerobic fitness can influence the salivary cortisol levels during exercise. Recommendations for future studies in this area on how to design a study to mitigate confounding variables are also discussed. **Health & Fitness Journal of Canada 2021;14(2):42-53**.
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Introduction

It is well known that living a physically active lifestyle is associated with physical and psychological health and well-being. As one becomes more physically active through engaging in regular exercise, their body experiences several physiological changes. Notably, routine physical activity will lead to an increase in cardiorespiratory fitness (Lin et al., 2015). This term is commonly reported in the literature as maximal aerobic power (VO2max), which is the greatest amount of oxygen that a person can consume and utilize per unit time typically measured in ml/min/kg. In addition to an increase in cardiorespiratory fitness due to aerobic training, several lines of evidence suggest that this form of exercise can lead to hypothalamo-pituitary-adrenal (HPA) axis adaptation in highly trained individuals (Duclos, Corcuff, Pehourcq, & Tabarin, 2001; Bernstein & McNally, 2017). The HPA axis is a neuroendocrine system consisting of the hypothalamus, pituitary gland, and the adrenal glands. The response of these organs in response to a stressor such as exercise plays a role in multiple regulatory processes within the body, notably the secretion of a glucocorticoid steroid hormone known as cortisol. The level of cortisol is typically

measured in participants through salivary sampling equipment in many laboratory investigations due to its non-invasive nature and validity (Obminski & Stupnicki, 1997). Moreover, salivary cortisol measures may provide a more accurate measure of the amount of unbound cortisol, which is the useful substrate to activate peripheral metabolism, in comparison to serum samples (Vining et al., 1983). The measure is commonly referred to as one's salivary cortisol level. Currently, there is generalized evidence that supports the idea that an increase in aerobic fitness will lead to an alteration in cortisol response during periods of physical or mental stress such as exercise (Rimmele et al., 2009; Rimmele et al., 2007). However, studies typically focussed on a single biological explanation or generalized their findings to a single level of exercise intensity (typically measured as a percentage of their heart rate reserve (HRR)). The primary purpose of this literature review is to summarize and critically evaluate the literature on 2 components of the cortisol response to physical activity: 1) to explain the differences in cortisol reactivity between three exercise intensity groups and 2) report potential biological explanations as to why an increase in aerobic fitness leads to a change in cortisol levels during exercise. Moreover, this literature review will aim to demonstrate the relationship between the studies to three different exercise intensities: low (30% HRR), moderate (50% HRR), and vigorous (70% HRR) intensities.

To understand the relationship between cortisol levels and exercise intensity, an explanation of the function of the hormone in the context of physical activity is required. As exercise intensity increases, the demand for energy in the form of adenosine triphosphate (ATP) increases to supply the working muscles and organs. One of the main substrates catabolized to produce ATP is glucose. The negative net energy balance triggers the activation of the HPA axis to begin the hormonal cascade to supply the body with additional energy substrates (Fuqua & Rogol, 2013). Cortisol plays a role in increasing blood glucose levels by increasing gluconeogenesis and glycogenesis in the liver (Baynes & Dominiczak, 2009). The increase in circulating energy substrates allows the body to endure prolonged or more intense bouts of physical activity.

Inter-Group Differences in Cortisol Response Based on Exercise Intensity and Duration

The response of the HPA axis to exercise is controlled by the intensity and duration to exercise (Duclos, Guinot, & Le Bouc, 2007). The stimulus for cortisol release from the adrenal glands seems to depend on meeting a threshold in exercise intensity. Several studies reported the minimum exercise intensity necessary to produce a cortisol response is approximately 60% of VO2max, or moderate activity for submaximal exercise (Duclos & Tamarin, 2010; Hill et al., 2008; Luger et al., 1987; Jacks, Sowash, Anning, McGloughlin, & Andres, 2002; Rudolph & McAuley, 1995; 1998). The variety of the cardiorespiratory fitness levels in the participants who partook in these studies suggest that intensity threshold for HPA axis activity is independent of their VO2max measurements. Once the threshold has been achieved, cortisol output and exercise intensity were observed to have a positive linear relationship, with a significant increase in cortisol output at higher submaximal work rates (Hill et al., 2008; Jacks et al., 2002;

Luger et al., 1987; Duclos, Corcuff, Rashedi, Fougere, & Manier, 1997; Duclos et al., 1997; Duclos & Tamarin, 2010). In contrast to a moderate-high workload, a cortisol response was only observed in low-to-moderate exercise intensities (40% VO2max) if the time interval lasted for approximately 90 minutes (Duclos et al., 1997; Sandoval, Guy, Richardson, Ertl, & Davis, 2004). These findings support the idea that the group exercising at the highest intensity will have the greatest salivary cortisol levels in studies where the running duration is only 30 minutes, not long enough to induce a significant duration-dependent cortisol response.

Another possible explanation for the intensity threshold for cortisol release stems from lactate, a by-product of glucose catabolism that occurs during exercise (Brooks, 1985). The increase in lactate becomes prominent at higher intensities of exercise when the anaerobic energy systems of the body is more heavily relied upon (Brooks, 1985). At a certain intensity of exercise, there will be a point where exceeding this workload will result in the exponential accumulation of lactate known as the lactate threshold (LT) (Ratamess et al., 2005). The literature suggests the exercise intensity required to meet the LT is around 55-65% HRR (McPartland, Pree, Malpeli, & Telford, 2010; Weltman et al., 1989). This exercise intensity level corresponds to the aforementioned intensity threshold required for cortisol reactivity in the HPA axis. Exercise intensity levels at or above LT is therefore associated with a marked increase in lactate compared to sedentary and low intensity groups. Lactate seems to influence the stimulation of the HPA axis to release cortisol during exercise (Kraemer & Ratamess, 2005). This finding is further supported in studies where exercising in high intensity musculoskeletal or aerobic protocols which elicit high lactate increases is associated with exercise-induced cortisol accumulation (Ratamess et al., 2005; Vega et al., 2006). The literature suggests that there is a positive association between lactate and cortisol release, providing further support that exercising at high levels of intensity triggers the increase in cortisol from the adrenal glands. However, none of the studies found a causal relationship between lactate and cortisol levels.

To make use of these findings, a conversion from %VO2max into %HRR is necessary. While some studies reported an insignificant relationship between %VO2max and %HRR (Dalleck & Kravitz, 2006; Swain, Leutholtz, King, Haas, & Branch, 1998), both the modality or the treadmill protocol is different from one study which used the Bruce treadmill protocol and found a significant relationship (Cunha, Midgley, Monteiro, & Farinatti, 2010). With respect to treadmill running utilizing a maximal exercise protocol based on the principles of the Bruce protocol, the finding of Cunha et al. (2010) provides support that the data collected in these studies can be converted from %HRR and %VO2max to be standardized to the previous findings in the literature regarding cortisol reactivity and %VO2max. Moreover, an additional study has reported a significant relationship between %HRR and %VO2max (Impellizzeri, Rampinini, & Marcora, 2005) lending support to the finding by Cunha et al. (2010). Therefore, based on the literature, it is expected that a vigorous (70% HRR) intensity group will have a significantly increased compared to both a low (30% HRR) and moderate (50% HRR). Only the highest intensity group will

exceed the intensity threshold required to observe a significant cortisol response.

The low and moderate groups do not meet the intensity threshold, or the duration required to elicit a cortisol response, hence it is expected that a nonsignificant change in glucocorticoid hormones will be observed (Sandoval et al., 2004). Multiple studies support the belief that exercising at 70% of one's maximal intensity is associated with a significantly greater cortisol response in comparison to 50% (Budde et al., 2010; del Corral, Mahon, Duncan, Howe, & Craig, 1994). Literature comparing the low (~30%HRR) and the moderate (~50%HRR) intensities review insignificant differences in cortisol concentration in exercises 60 minutes or less in duration (Jacks et al., 2012; Sandoval et al., 2004). Moreover, the results from Sandoval et al. (2004) reported that participants in the 30%VO2max and 50%VO2max groups had a lower mean cortisol in comparison to the control group which did not exercise. Engaging at low intensity exercise at 38.0±2.09%VO2max was associated with a significant reduction in cortisol levels after controlling for plasma loss due to physical activity (Hill et al., 2008). One suggested mechanism explaining the reduction in cortisol levels is that low intensity exercise may increase the metabolic clearing rate of the hormone by target tissues in the body (Davies & Few, 1973). When reviewing the literature, methodologies pertaining to timing of cortisol sample collection were assessed to ensure that valid concentrations were collected which accurately reflect the true activity of the HPA-axis. Kirschbaum and Hellhammer (1994) suggested that peak concentrations of cortisol occur during the 10-15-minute interval during the exercise bout, and at least for 30 minutes post-exercise. Based on the literature, it is suggested that the low and moderate intensity groups will have an insignificant rise in cortisol response, and in fact, a reduction in circulating cortisol levels in compared to sedentary controls due to failure in meeting the intensity threshold of 60% HRR required to elicit an HPA axis response to secrete cortisol and due to increased metabolic clearance of the hormone. Figure 1 illustrates the difference in cortisol levels between the low intensity group and the high intensity group adapted from McGuigan, Egan, and Foster (2004). A similar trend is expected to be observed in relative cortisol levels between the three exercise intensity groups regardless of the participant's cardiorespiratory fitness level as the intensity threshold remains at around 60%HRR which is higher than the low and moderate workloads.

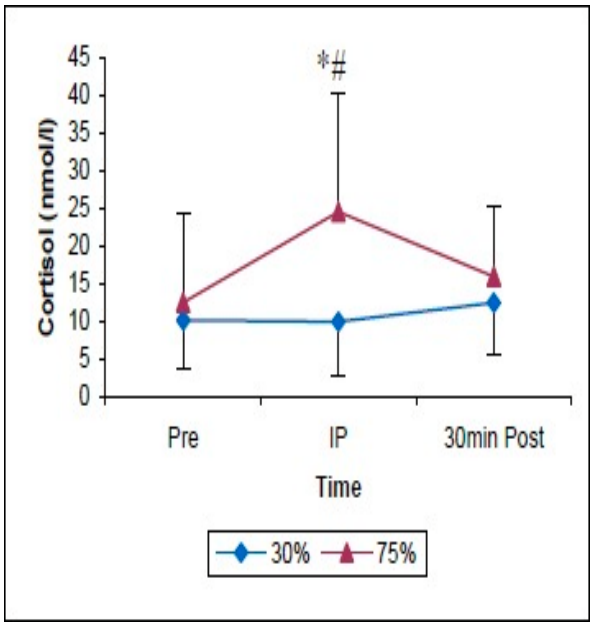

Figure 1. Adapted from McGuigan, Egan, & Foster (2004). Mean salivary cortisol concentrations (±SD) before exercise, immediately following exercise and at 30 minutes of recovery (n = 10) at 30% and 75% of the subjects' maximal exercise intensity. * denotes significant differences between exercise time points. # denotes significant

differences between the low intensity and high intensity exercise sessions.

Effect of Cardiorespiratory Fitness on Cortisol Response to Exercise

An increase in regular aerobic training will lead to increased cardiorespiratory fitness typically measured in VO2max in ml/kg/min. In addition to the health benefits that come with an increase in fitness levels (Warburton, Nicol, & Bredin, 2006), several lines of evidence provide support to the idea that the HPA axis undergoes an adaptation in response to repetitive stressors in the form of physical activity to alter its cortisol response (Duclos & Tabarin, 2010; Mastorakos & Pavtlatou, 2005; Rimmele et al., 2009). There is evidence that supports an increase in cortisol levels in highly trained individuals. One assumption made with highly-trained individuals is that they would have a higher VO2max value compared to sedentary and recreationally active persons based on the amount of physical activity performed regularly measured on non-exercise questionnaires that provide useful estimations but have questionable validity (Bilek, Venema, Willett, & Lyden, 2008; Davidson & de Morton, 2007). On the contrary, there are other studies that report a reduced cortisol level in highly trained individuals compared to persons who are less physically active. The following paragraphs will examine the literature from both sides of the argument.

On one hand, there is evidence suggesting that individuals with increased cardiorespiratory fitness elicit an increased cortisol response compared to less fit persons (Marthur et al., 1986; Luger et al., 1987). The findings by Luger et al. (1987) noted that only highly trained exercise subjects reported highly elevated cortisol levels consistent with mild hypercortisolism. Their study concluded that an alteration in the HPA axis was a contributing factor to the observed increased cortisol. A further investigation into the mechanisms of the HPA axis is warranted to uncover the cause of the effect of fitness on HPA axis adaptation.

The HPA axis operates on feedback mechanisms (Panagiotakopoulos & Neigh, 2014). When a stressor such as intense physical activity is detected by the hypothalamus, its paraventricular neurons secrete corticotropin-releasing hormone (CRH) which is circulated to the anterior lobe of the pituitary gland (Panagiotakopoulos & Neigh, 2014). CRH interacts with the receptors of the anterior pituitary gland and stimulates the secretion of adrenocorticotropic hormone (ACTH) into the bloodstream (Panagiotakopoulos & Neigh, 2014). The circulated ACTH then reaches the adrenal cortex of the adrenal gland at the kidneys and interacts with its receptors to stimulate the biosynthesis of cortisol and other corticosteroids (Panagiotakopoulos & Neigh, 2014). A visual representation of the HPA axis mechanisms is provided in Figure 2 (Panagiotakopoulos & Neigh, 2014).

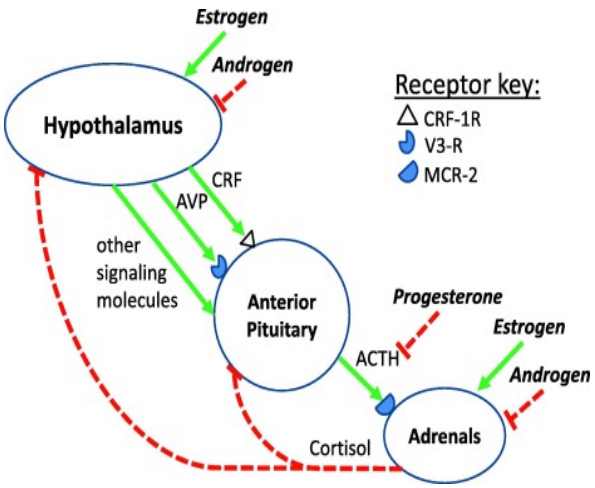

Figure 2. Adapted from Panagiotakopoulos & Neigh (2014). Overview of the HPA axis – Stimulatory inputs are depicted in green arrows and inhibitory signals in dashed red lines. Androgen hormones will not be discussed in detail in this report.

One important mechanism is the negative feedback interaction between secreted cortisol and its inhibitory effect on the hypothalamus and the pituitary gland to release CRH and ACTH respectively. There is evidence that endurance-trained individuals will have a demonstrated lowering of sensitivity to the negative feedback of cortisol in the pituitary gland (Duclos & Tabarin, 2010; Duclos et al., 2001). Moreover, regular transient HPA-activation through physical activity in highly trained individuals seems to decrease corticotropic sensitivity to negative feedback due to a reduction of cortisol receptors (Heuser et al., 1991; Sapolsky, 1993). This decrease in negative feedback in endurance-trained individuals would ultimately lead to continued ACTH release and subsequent cortisol secretion at a higher rate than non-highly trained persons.

In addition to the inhibition of the negative feedback mechanism, endurance training seems to influence the magnitude of ACTH release in response to exercise, where there is contradicting evidence on whether salivary cortisol increases or decreases with an increase in cardiorespiratory fitness levels. A study reported an increase in both ACTH and cortisol levels after an hour of intense exercise in highly trained athletes compared to control subjects (Carr et al., 1981). The results suggest an adaptation in the HPA axis because of aerobic training. This contradicts a finding from a longitudinal study which compared participants before and after a 12-week aerobic exercise program which elicited a mean 11% increase in VO2max post-intervention. The investigation reported that the ACTH response to exercise at the same %VO2 led to a blunted ACTH secretion following aerobic training (Buono, Yeager, & Sucec, 1987). This attenuation of ACTH response to exercise is believed to lead to a reduced cortisol output by the adrenal glands. However, a reduction in ACTH may not necessarily lead to a causal reduction in cortisol as it has been observed that elevated levels of this hormone did not lead to a significant increase in cortisol levels in highly trained male participants (Inder et al., 1995). One possible explanation suggested was that the adrenal gland sensitivity to ACTH may be reduced in endurance-trained males (Duclos et al., 1997). This suggests that there are likely other mechanisms that influence the release of cortisol.

While there is inconclusive evidence that endurance-trained individuals have a significantly increased or decreased cortisol level at higher intensities of exercise, it is suggested that the full explanation is multifactorial and not a single variable can fully explain the difference. There are certainly notable discrepancies with regards to the methodology in the vast number of studies. The protocol of the exercise varied in modality (treadmill, cycle ergometer), duration (15-90 minutes), intensity (%HRR or %VO2max variation), and the timing in which the cortisol samples were taken. The rigor in which studies controlled for potential confounding variables were also inconsistent. The use of psychological screening for psychological illnesses such as depression and anxiety were seldom used. Illnesses such as major depressive disorder or anxiety disorders can cause a

change in cortisol levels (Burke, Davis, Otte, & Mohr, 2005; Vreeburg et al., 2010).

In addition, the time of day in which the data collection occurred varied between studies. The diurnal rhythm plays a role in the amount of cortisol secreted (Ockenfels et al, 1995), and an absence of a standardized collection time leads to results that cannot be directly compared. Nutrition status seems to influence cortisol levels during exercise (Kraemer et al., 2005). Their investigation suggested that supplementation of specific antioxidants or nutrients such as vitamin C can attenuate the cortisol response to physiological stress. Further evidence indicates that carbohydrate levels can also influence exercise-induced cortisol response (Mitchell et al, 1998). Consuming low-carbohydrate diets as opposed to high-carbohydrate diets before endurance exercise correlated to significantly increased plasma cortisol levels. Incorporating a standardized meal a few hours prior to cortisol sampling would be a prudent consideration in developing the investigation protocol. One protein, however, found to have no significant influence on cortisol levels was BDNF (Moreira et al., 2018). The study by Moreira et al. (2018) postulated that elevated BDNF levels in athletes from pre to post competition resulted from the players' regular exposure to stress-inducing situations in lieu of cortisol levels. Lastly, climate acclimatization to the physiological stressor during aerobic activity can also influence cortisol response (Izawa et al., 2009). Exercising in either familiar or non-familiar ambient temperatures was observed to attenuate or amplify cortisol response, respectively.

It should also be noted that the various studies examined in this review largely employed male subjects of similar ages. To assess potential biases posed by the limited participant demographic, the effects of androgens and participant age on exercise-induced cortisol response should be considered. In highly trained men, submaximal exercise-induced plasma cortisol levels were observed to decrease as age increased (Silverman & Mazzeo, 1996). Furthermore, evidence suggests that both endogenous and exogenous cortisol, such as that aroused by aerobic activity, suppresses testosterone secretion at the testis (Brownlee, Moore & Hackney, 2005; Rubinow et al., 2005). Notably, this study also reports the regulatory behaviour of testosterone on the HPA axis. A subsequent study suggested that cortisol's inhibitory effect on the adrenal-testicular axis is a reproductive adaptation to stress (Cumming, Quigley & Yen, 1983). In women, it was observed that exercise-induced cortisol levels were independent of menstrual phase but affected by menstrual status (Kanaley et al., 1992). The investigation by Kanaley et al. (1992) observed that amenorrhoeic participants displayed much greater exercise-induced cortisol responses than their eumenorrheic counterparts. This finding suggests that exercise-induced cortisol levels correlated to hormonal disturbances to the HPA axis.

Lastly, the sample sizes of most of studies were small, with a range between 8-15 being the most common. Future studies should consider 1) large sample sizes; 2) rigorous screening processes for participants; 3) frequent cortisol sampling; and 4) control for various confounding variables associated with deviations in cortisol response to ensure that a more accurate and precise finding is collected.

Conclusion

Based on our findings, cardiovascular fitness seems to have no influence on the

exercise intensity threshold required to elicit a cortisol response, hence the intensity threshold seems to be around 60%HRR (McPartland, Pree, Malpeli, & Telford, 2010; Weltman et al., 1989). The low and moderate intensity groups are 30%HRR and 50%HRR respectively, and since the period of exercise is less than the duration required to activate the cortisol response, the observed glucocorticoid hormone level will be either an insignificant change or a slight decrease in comparison to baseline measures at rest due to metabolic clearance. Both the low and medium exercise intensities do not seem to be significantly different from each other. The vigorous intensity group exercises at 70%HRR, which exceeds both the lactic and intensity threshold required to observe a marked increase in lactate which seems to influence cortisol release, in addition to a direct cortisol response from the HPA axis. Whether an increase in aerobic fitness measured by VO2max leads to an increase or decrease in cortisol at vigorous intensities of exercise is inconclusive. Individual mechanisms such as reduced sensitivity to ACTH for positive feedback, or the attenuation of anterior pituitary sensitivity to cortisol leading to reduced negative feedback of adrenocorticotropin contributed to an increase and decrease in glucocorticoid levels respectively. Most investigations in this field have small sample sizes of less than 15 and have a difference in methodology, making it difficult to draw common conclusions. The lack of consensus suggests that there are additional factors, where some were briefly discussed, that influence the magnitude of cortisol levels during intense bouts of exercise that need to be rigorously examined in future investigations.

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Authors' Qualifications

The authors' qualifications are as follows: Phillip Do, BKIN, JD (c); Flora Guo, BASc (c); Darren Warburton, MSc, PhD, HFFC-CEP.

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