A·S·P

ADRENOCORTEX STRESS PROFILE

SUPPORT GUIDE

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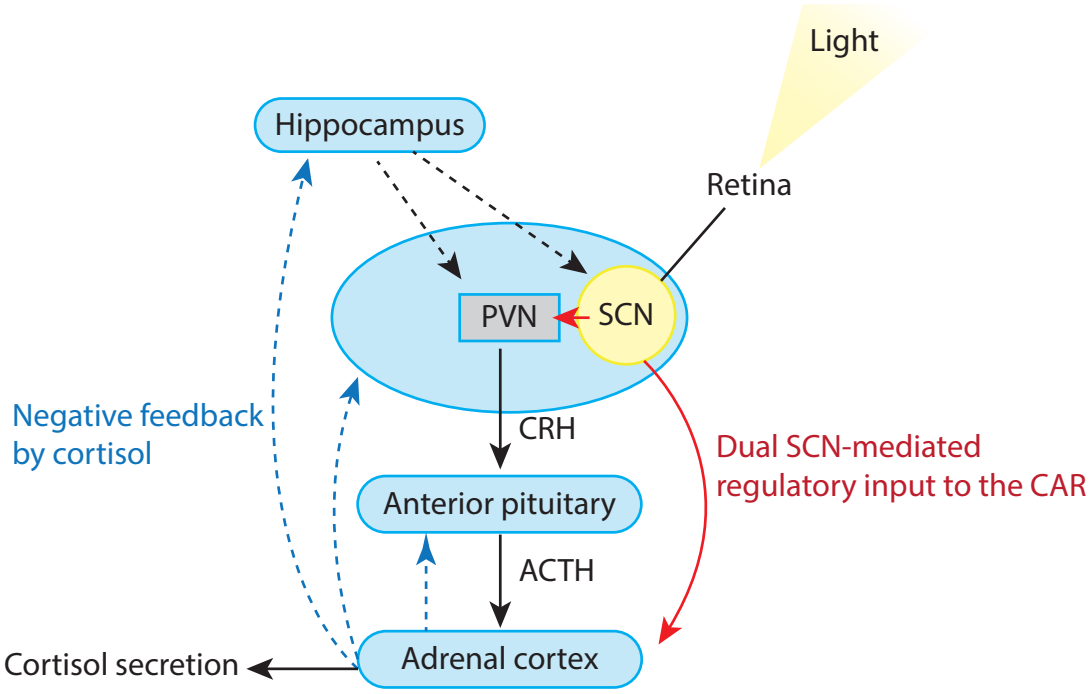
Hypothalamic-Pituitary-Adrenal (HPA) Axis and the Stress Response:

In response to any stressor, the hypothalamus produces corticotropin releasing hormone (CRH), which stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH). ACTH triggers the release of glucocorticoids (cortisol) from the adrenal cortex. These glucocorticoids then play an inhibitory role, signaling the system to shut down the stress response via negative feedback. Under optimal conditions, glucocorticoids help the body to maintain homeostasis and play a role in immune activity, growth, reproductive functions, and energy metabolism.



Cortisol shows a strong diurnal rhythm peaking within the first hour after awakening, declining rapidly over the morning hours, and then tapering off over the rest of the day before reaching its lowest point at night.[2]

In addition to this well-described diurnal cycle, there is a brisk increase of cortisol levels within 30 minutes of awakening in the morning. This phenomenon is termed the **cortisol awakening response (CAR).**[3]

CAR is what its name implies: a physiological response to awakening. It is a discreet and distinct component of the cortisol circadian cycle, unrelated to those of cortisol secretion through the rest of the day. CAR represents the momentum of rising cortisol levels that begins several hours prior to awakening and an additional transient increase of up to 50%. The initial cortisol rise begins due to ACTH-mediated normal HPA axis activities with the additional CAR increase caused by supra-chiasmic nucleus light activation. CAR may play a role in the transition from sleep to full alertness, transcribing a time of day message to the immune system. Therefore, CAR is an independent marker of central biological clock function and overall HPA axis resiliency.[4]

Patient Population:

The symptoms of HPA axis dysfunction can be vague and highly variable. The Adrenocortex Stress Profile may be useful in patients who present with fatigue, insomnia, weight gain, depression, GI complaints, and chronic pain. HPA axis dysfunction is associated with many disease processes, including, but not limited to:

- Hypertension
- Cardiovascular disease
- Gastrointestinal and immune dysregulation
- Diabetes and metabolic syndrome
- Depression
- Chronic fatigue
- Persistent pain
- Neurodegenerative disease and cognitive decline[2,7-14]

Physical, emotional, and mental stressors, both real and perceived, contribute to overall allostatic load, which leads to adjustments in the body's HPA axis regulatory 'set points.' Daily hassles, chronic pain, blood sugar dysregulation, work overload, and poor relationship quality can alter the HPA axis and can translate into compromised immune function, increased disease risk, psychosocial disturbances, and shortened longevity.[2]

- The **Adrenocortex Stress Profile (ASP)** offers an assessment of the Hypothalamic-Pituitary-Adrenal (HPA) axis using carefully timed salivary samples of the hormones cortisol and DHEA. Four salivary samples measured throughout the day can give insight into cortisol's natural circadian diurnal rhythm.
- The **Cortisol Awakening Response (CAR)** can be added to the ASP by providing two additional awakening salivary samples to reflect HPA axis resiliency and provide the most comprehensive look at cortisol and the HPA axis.

Cortisol:

It is important to understand the overall pathophysiology of the stress response. A number of mechanisms contribute to disease in chronic stress.

- CRH plays an important role in inhibiting gonadotropin releasing hormone (GnRH) secretion. It also inhibits growth hormone (GH), thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH). Therefore, the stress response includes suppressing reproductive, growth, and thyroid functions.[5]
- Glucocorticoids themselves directly inhibit gonadotropin, GH, and TSH secretion and render their target tissues resistant.[5]
- Glucocorticoids also suppress 5' deiodinase, which converts the inactive tetraiodothyronine (T4) to the active triiodthryonine (T3).[5]
- Glucocorticoids stimulate hepatic gluconeogenesis. They also inhibit insulin actions on skeletal muscle, while potentiating insulin action on adipose tissue. This leads to visceral adiposity and metabolic syndrome. Because of increased hepatic gluconeogenesis and the above described insulin resistance, activation of the HPA axis may contribute to the poor control of diabetic patients during periods of emotional stress or inflammatory diseases.[5]
- Glucocorticoids also have direct effects on the bone by inhibiting osteoblastic activity, which leads to "low turnover" osteoporosis.[5]
- HPA axis dysfunction is also implicated in altering the gastrointestinal mucosa, modulating GI motility, immunity, permeability, and the microbiome.[6]
- Cytokines and other humoral inflammatory mediators are potent activators of the central stress response. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β, and interleukin-6 (IL-6), can cause HPA axis stimulation alone, or in synergy with each other. There is evidence that IL-6 plays the major role in HPA axis immune stimulation, especially in chronic inflammatory stress.[5]
- Cortisol inhibits all components of the immune reponse, which increases infection risk and protects against autoimmune reactions.
- Chronic, maladaptive HPA axis response (low cortisol) mimics a glucocorticoid-deficient state, leading to relative resistance to infections and increased autoimmune susceptibility.[5]

As demonstrated by these systemic effects, HPA axis dysfunction is seen as a root cause for disease; therefore, comprehensive HPA axis evaluation is very important.

DHEA:

Dehydroepiandrosterone (DHEA) is the most abundant circulating steroid hormone in the body. It is made and secreted in the adrenal cortex zona reticularis and can be made in the brain as a neurosteroid. DHEA can be converted downstream in the steroidogenic pathway to create androgens and estrogens. DHEA concentrations peak at around age 25 years and then decline steadily over the following decades.[34]

DHEA has many neurobiological actions, such as neuroprotection via the blocking of neurotoxic effects, and supporting neurogenesis. DHEA can also influence apoptosis, catecholamine synthesis, and secretion. It has antioxidant and anti-inflammatory properties and can be protective against corticosterone's neurotoxic effects.[35]

Some labs measure the sulfated form of DHEA as DHEA-s. DHEA-s represents a more stable and larger DHEA pool in the body. DHEA is a neutral steroid and passes rapidly from the blood to the saliva by passive diffusion. DHEA-s is a charged, polar molecule and cannot diffuse easily through lipid membranes into saliva. Salivary DHEA is considered a surrogate marker for DHEA-s.[38]

DHEA:Cortisol Ratio:

The ratio of DHEA to cortisol is calculated based on collection of the 60 minute post awakening (7:00 AM – 9:00 AM) sample. This calculation represents a measurement of anabolic and catabolic balance. Since DHEA acts not only as an anabolic hormone, but appears to function to down-regulate the cellular effects of cortisol, this measurement can theoretically enhance the predictive value of HPA axis dysfunction.[38]

The clinical interpretation of the Adrenocortex Stress Profile involves:

1. Timed Cortisol Measurements
2. Overall Diurnal Rhythm/Slope
3. Cortisol Awakening Response
4. DHEA
5. DHEA:Cortisol Ratio

Timed Cortisol Measurements:

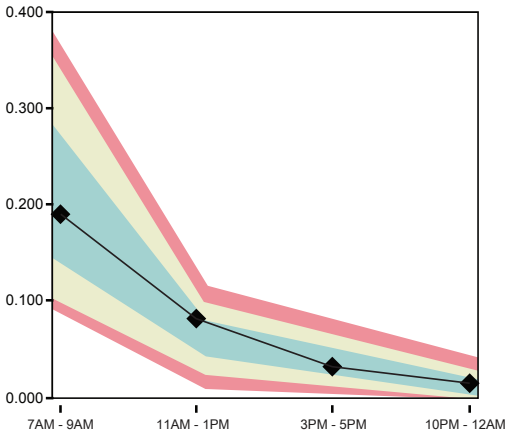
Specific cortisol findings throughout a diurnal rhythm may be affected by any number of acute mental, emotional, and physical daily stressors. Abnormal results should be correlated with each patient's clinical presentation and daily routine.[2,16]

TIMING	SIGNIFICANCE	CONSIDERATIONS WHEN HIGH	CONSIDERATIONS WHEN LOW
Cortisol Awakening Response (CAR) Add-on	HPA axis resiliency Perception of control around chronic stress[17]	Adaptive anticipation of daily stress Stimulation of motor function, immune response, and alertness[4,18]	Burnout, depression, PTSD, chronic fatigue syndrome, early loss experiences, material hardship, amnesia, hippocampal damage, non-response, abnormal sampling[15,4,18,19]
Morning **7:00AM-9:00AM**	Peak ACTH-mediated adrenal gland response	Exercise, blood sugar dysregulation, lifestyle stressors, pain	Inability to mount peak response due to HPA axis dysfunction and/or down regulation from chronic stressors
Midday **11:00AM-1:00PM**	Adaptive function of the HPA axis to daily routine	Exercise, blood sugar dysregulation, lifestyle stressors, pain	HPA axis dysfunction
Afternoon **3:00PM-5:00PM**	Can reflect glycemic control	Exercise, blood sugar dysregulation, lifestyle stressors, pain	HPA axis dysfunction
Evening **10:00PM- 12:00AM**	Baseline HPA axis function	Stress, alcohol, exercise, lifestyle stressors, pain Linked to insomnia and various diseases such as diabetes, cardiovascular disease, hormonally-driven cancers, and osteoporosis[18,20-24]	Optimal

Treatment Options:

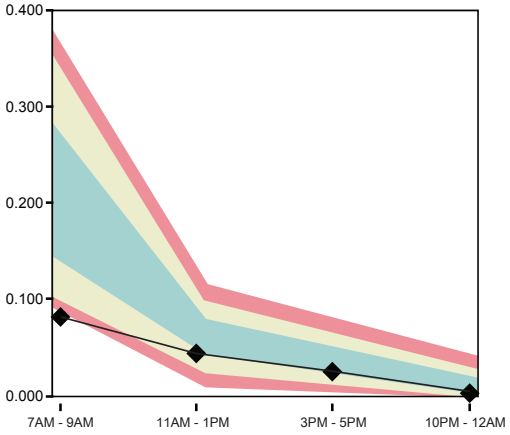
Treatment of abnormal cortisol should be directed at the stressor's root cause. Lifestyle modification with relaxation methods, dietary changes, pain management, and overall HPA axis support with nutrition, adaptogens, and supplements can be helpful.[25]

Normal Diurnal Slope



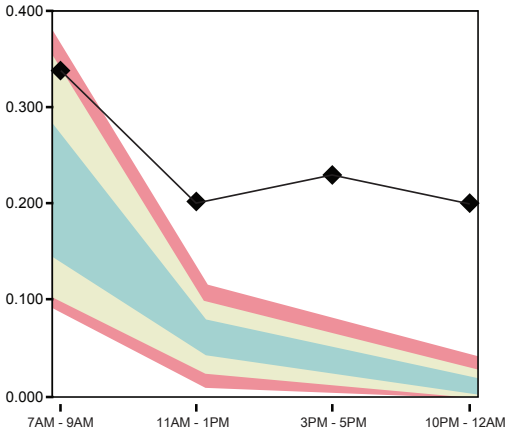
The natural cortisol diurnal rhythm shows a peak within the first hour after awakening, a rapid decline over the morning hours, and then tapering through the rest of the day before reaching its lowest point at night.[2]

Low Slope



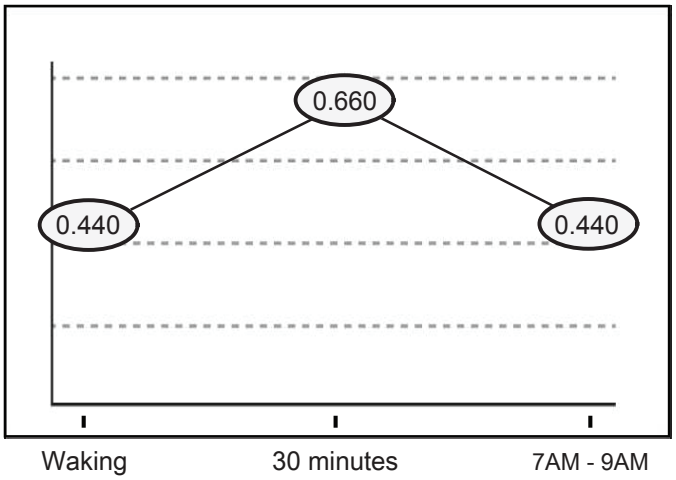
- Chronic stress burden
- Poor psychosocial function
- Lack of HPA axis resiliency
- Lower perceived control over stress
- Post-Traumatic Stress Disorder (PTSD)
- Persistent fatigue, anxiety, and depression
- Predictive of health outcomes, such as increased breast cancer mortality, increased coronary calcifications, and increased body mass index[2,3,15]

High Slope



- Appropriate response to a major stressor
- Perceived insurmountable challenge[15]

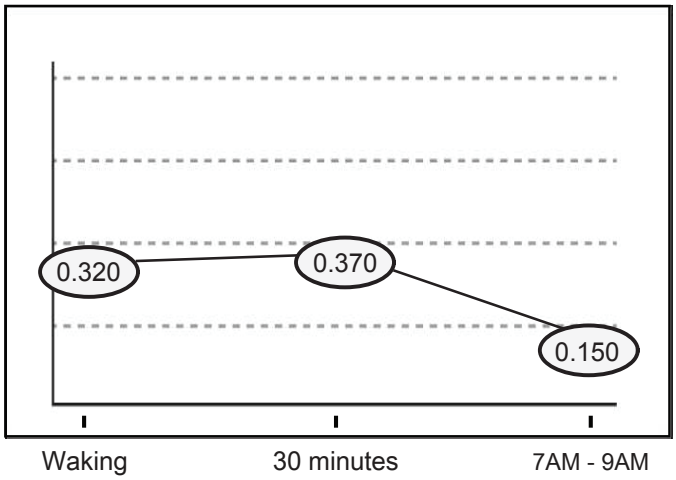
Cortisol Awakening Response (CAR) Add-On



Percent Increase	50	Expected: >50%

CAR reflects a person's ability to cope with anticipated challenges and the perceptions of control around chronic stress. CAR is calculated as a direct percent increase. A value of at least 50% is expected.[3,4,17,19,26]

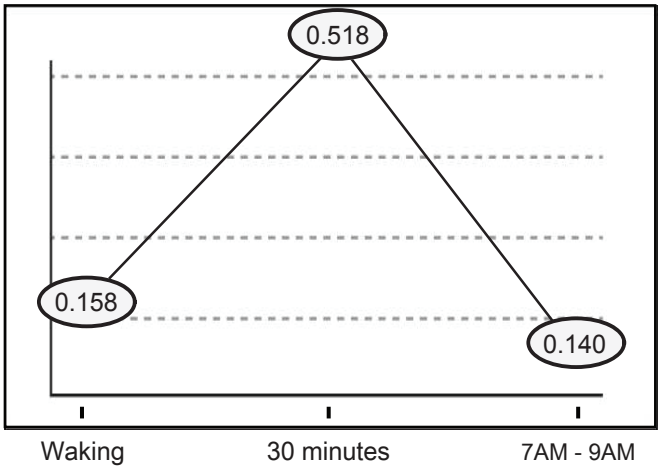
Blunted CAR



Percent Increase	16	Expected: >50%

- Burnout
- Depression
- PTSD
- Chronic Fatigue Syndrome
- Self-reported health problems
- Early loss experiences
- Material hardship
- Amnesia
- Hippocampal damage[4,18]

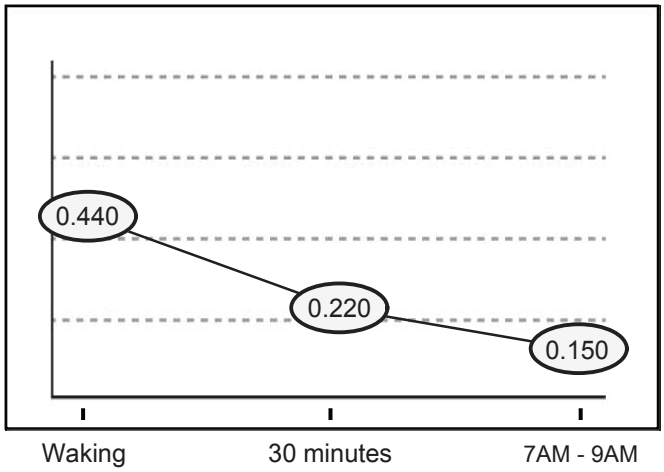
Elevated CAR



Percent Increase	228	Expected: >50%

- Adaptive anticipation of daily stressors ("preparing for action")
- Stimulation of motor function, immune response, and alertness[4,18]

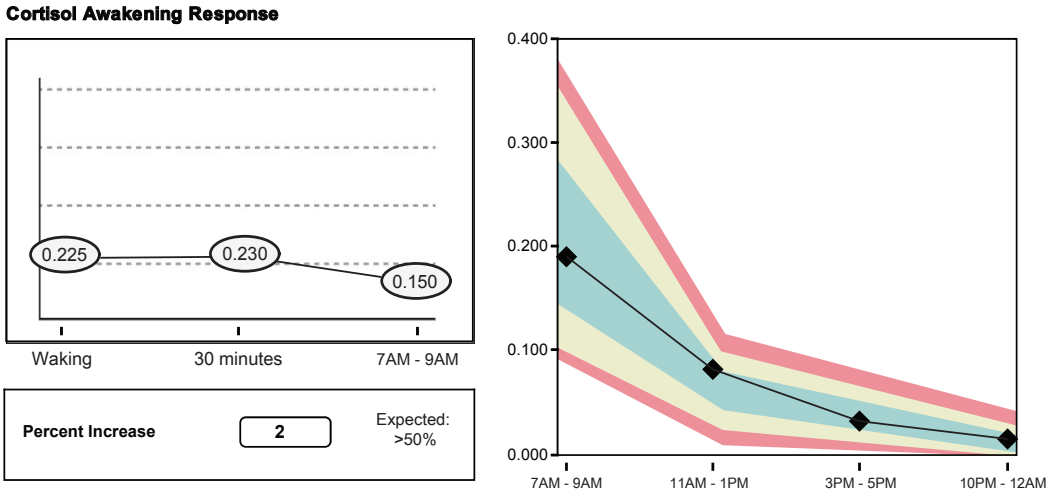
Negative CAR



Percent Increase	-50	Expected: >50%

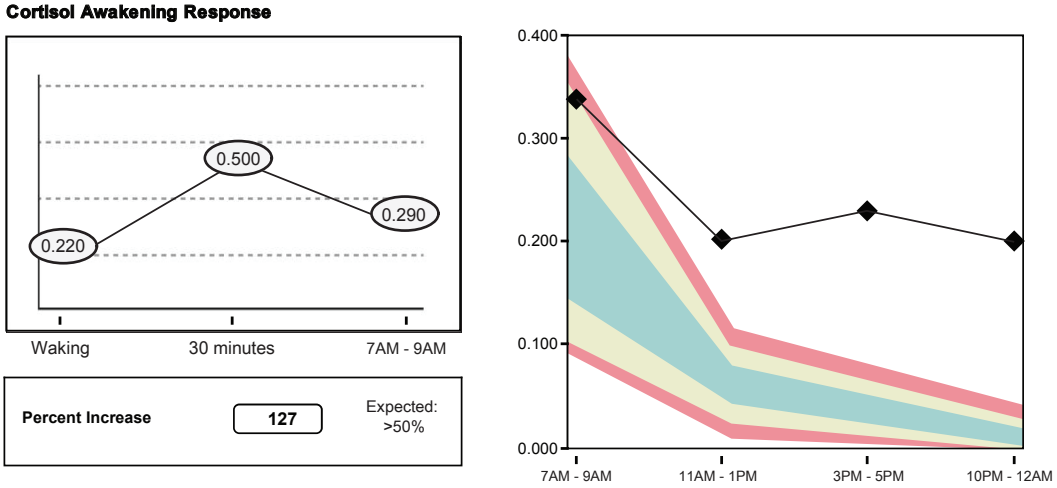
- Ensure there was no delay between waking and obtaining the first sample
- Literature is evolving regarding clinical implications[27,28]
- One hypothesis is that a negative CAR percentage may reflect a blunted CAR with further loss of resiliency

CAR Non-Response



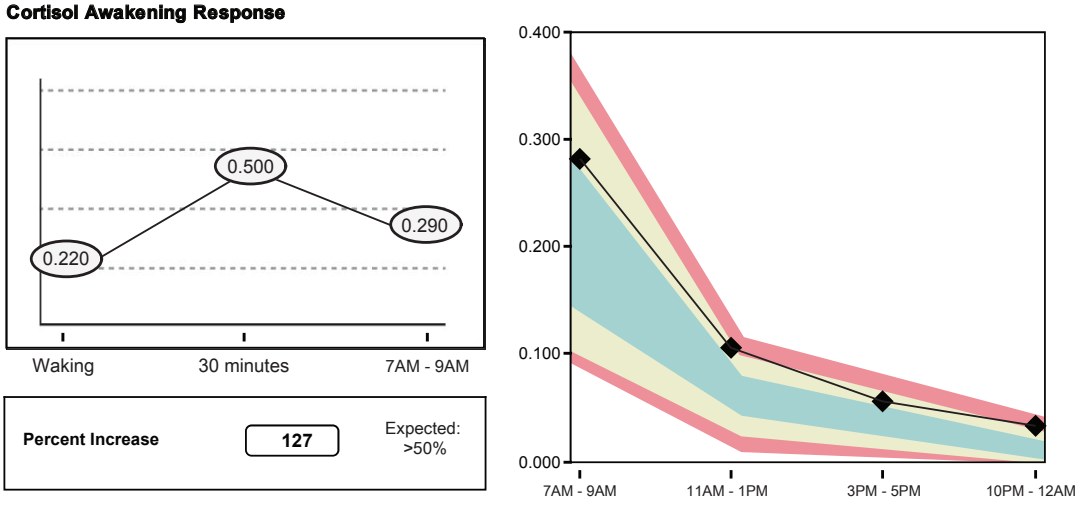
- 25% of healthy adults do not mount a CAR
- Response is defined as an increase of at least 0.09µg/dL above individual baseline with otherwise adequate cortisol diurnal curve
- Ensure proper sampling[17,19]

CAR Elevated with High Slope



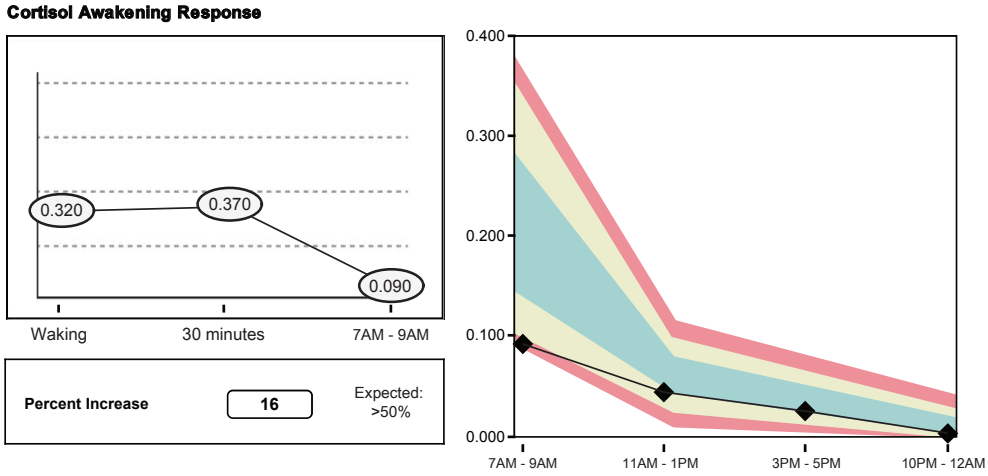
- General HPA axis dysfunction
- Significant stressor, real or perceived[26,29]

CAR Elevated with Elevated Slope



- Anticipation and reflection of daily stress
- Overall total cortisol levels during CAR are predictive of relative mean cortisol levels throughout the day[26,30]

CAR Blunted with Low Slope



- Generalized HPA axis dysfunction
- Burnout
- Chronic stressor[26,30]

DHEA	
HIGH:	Exogenous exposure, supplementation, polycystic ovary syndrome, adrenal hyperplasia, and adrenal tumors[31-35]
LOW:	Advancing age, chronic stress, HPA axis dysfunction Low DHEA levels have been associated with immune dysregulation, cardiovascular disease, arthritis, osteoporosis, insomnia, declining cognition, depression, fatigue, and decreased libido.[31-35]

DHEA:Cortisol Ratio	
HIGH:	Favors anabolic activity Address specific cortisol and DHEA abnormalities[32,36-38]
LOW:	Favors catabolic activity Address specific cortisol and DHEA abnormalities[32,36-38]

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