



Review Article

Anxiety disorders in patients with cardiopulmonary diseases: A brief review

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ABSTRACT

This manuscript reviews the current literature involving clinical anxiety and cardiopulmonary disease, considers the hypothesized physiological mechanisms for anxiety, and discusses the use of exercise as a treatment for both anxiety and cardiopulmonary diseases. The literature summary consists of original investigations, meta-analysis, commentaries, and review publications in order to better understand the biological and psychological mechanisms for using exercise as treatment and to provide details specific to cardiopulmonary disease and anxiety management. A gap in the literature exists concerning the anxiolytic effects of exercise as a psychological and physical treatment in cardiopulmonary populations. The findings from this review support further investigation into the use of exercise to ameliorate the burden of anxiety in cardiopulmonary disease patients.

This review evaluates the current literature surrounding cardiopulmonary disease and anxiety. A systematic literature search identified articles discussing the prevalence, association, and risk of anxiety in cardiopulmonary patients. Though depression is often studied in this population, recent investigation supports a need for further research regarding anxiety in cardiopulmonary patients. Treatment to manage patients' psychological profile can reduce exacerbations of known disease, reduce hospital readmission, and improve functional capacity, and overall quality of life.

Introduction

Chronic diseases are a leading cause of death globally.¹ The Center for Disease Control and Prevention (CDC), American College of Sports Medicine (ACSM), and National Institute of Health (NIH) report cardiac and pulmonary diseases (excluding lung cancer) as the first and fourth leading causes of death respectively. Currently, coronary artery disease (CAD) accounts for many cardiovascular related disease related deaths while chronic lower respiratory disease and primary chronic obstructive pulmonary disease (COPD) account for most pulmonary disease related deaths.^{2–4}

Cardiopulmonary diseases often develop as a result of poor lifestyle.^{1–4} Unfortunately, the average American makes daily choices detrimental to health while modern convenience contributes to poor lifestyle choices.⁵ Following CAD or COPD diagnosis, patients are at an elevated risk for depression and anxiety. The inclusion of anxiety into a patient's risk profile is relatively uncharted, promoting researchers and clinicians to question when a patient's anxiety becomes pathological and not just reaction to diagnosis.

A literature search conducted through Pubmed and Medline

databases identified exercise studies in cardiopulmonary disease populations where qualitative measures of anxiety were included. This review examines the current research involving the prevalence and pathogenesis of anxiety in cardiopulmonary diseases and discusses exercise as a treatment option.

Anxiety in the cardiopulmonary patient

Anxiety increases significantly following diagnosis of cardiopulmonary disease as demonstrated in several studies.^{6–8} As evidence accumulates, scientists better understand the importance of assessing both anxiety and depression in patients with cardiovascular disease. For example, Kunik et al. evaluated 1334 COPD patients and found 65% met the diagnostic criteria for depression and/or an anxiety disorder, but only 31% received anxiety treatment as demonstrated in Fig. 1 which implies that a large group of patients is not receiving anxiety treatment.⁹

One possible source of anxiety for cardiopulmonary patients is the experience of dyspnea. Even when symptoms are not present, residual anxiety lingers regarding a fear of shortness of breath and a feeling of helplessness. As a result, exercise and functional capacity decrease and a

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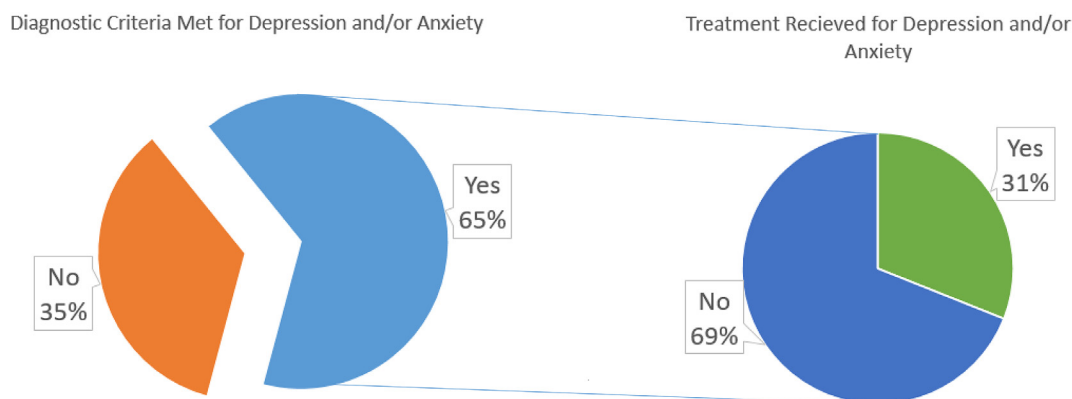


Fig. 1. Depression and/or Anxiety in COPD Patients. In 1 334 COPD patients evaluated for depression and anxiety, Kunik et al. found 867 patients (65%) to meet the diagnostic criteria for clinical depression and/or anxiety. Of those 867 patients, only 269 (31%) received psychological treatment. The information for developing this figure comes from Kunik et al. *Chest*. 2005 (Reference 9).

person avoids physical activity.¹⁰ Present knowledge about anxiety and depression comes from observational studies conducted within clinics and hospital settings. Very few studies are conducted in a community setting posing the concern that anxiety levels are perhaps greater than estimated through hospital-based studies. When not receiving secondary preventative care aside from pharmacological management for cardiopulmonary diagnoses, patients are even less likely to receive psychological treatment. These circumstances can exacerbate the effects of anxiety as a person becomes more socially isolated.

Determining the true prevalence of mood disorders, particularly anxiety, is difficult due to the social stigma of mental illness. Many cases go undetected or unreported because healthcare workers are not trained to see the signs and symptoms, and patients are not likely to seek help.¹¹

Following a diagnosis for a chronic disease exacerbated by poor lifestyle choices, patients easily feel shame, guilt, and anger regarding their condition. Frequently these emotions mask a deeper fear of the future, lack of independence, and even death.¹² Often these emotions cause the patient to withdraw and reject support. Repression of fear and guilt can manifest into chronic anxiety which negatively impacts both physical health and quality of life.¹²

Yohannes et al. found that COPD patients' quality of life is more strongly associated with psychological health status than lung function.¹⁰ In a cross-sectional analysis, COPD patients with anxiety and depression reported lower functional capacities than patients with only COPD when controlling for lung function.¹⁰

Cohen et al. completed a comprehensive review with similar results for cardiac patients with CAD and heart failure.¹³ When controlling for objective measures of cardiac function (i.e., ejection fraction), patients with depression and anxiety are more likely to report greater physical limitations and lower quality of life.¹³ Also, whether anxiety precedes cardiovascular disease or vice-versa is still in question. Presently, no definitive evidence exists supporting one process over the other. Persons with anxiety show elevated sympathetic activation suggesting an increased cardiac demand via vasoconstriction and perhaps augmenting the atherosclerotic process.¹⁴ A cross-sectional study conducted by Vogelzangs et al. found persons with an anxiety disorder showed a threefold increase in prevalence of CAD.¹⁵ When compared to the prevalence of anxiety in the general population, CAD patients are at a threefold greater risk for developing anxiety following their diagnosis.¹³

In this regard, teasing apart which condition is the primary risk factor is difficult. Studies evaluating the association of anxiety and cardiopulmonary diseases are often retrospective in nature. Such analyses are limited in the ability to discern the pathological sequence because of the overlap in symptoms between conditions such as COPD, heart failure, and anxiety or depression.¹⁰

Current information provides strong evidence for continuing scientific investigations into the relationship between cardiopulmonary disease and mood disorders. To date, a greater volume of literature exists for analyzing depression and chronic disease. Only recently have researchers begun to explore anxiety as an independent risk factor. Anxiety increases in cardiopulmonary disease populations will need to be evaluated to improve the detection, provide proper treatment, improve quality of life, and mitigate the economic burden of reduced functional capacity attributed to cardiopulmonary diseases.

Anxiety as a response and a risk factor

Much discussion has taken place concerning the etiology of anxiety, leading scientists to propose various psychological and physiological mechanisms. Recent evidence has focused on the relationship of anxiety with chronic disease. The stress diathesis model was developed to more simply explain the development of psychological disorders.¹⁶ This model links a stimulus such as chronic disease diagnosis with the manifestation of an anxiety disorder in a person with an underlying predisposition for mood disorders. In other words, a person's susceptibility for anxiety is manifested by diagnosis of a physical illness.¹⁴

Persons coping with anxiety may experience heightened anxiety sensitivity and exaggerated fear response behaviors.¹⁶ Turk using the stress diathesis model to address chronic pain in patients applied the same principles to anxiety management.¹⁶ A person having anxiety and cardiopulmonary disease is inclined to avoid stressors believed to trigger a cardiac or pulmonary event such as physical activity. While attempting not to stress their heart or lungs and avoid a racing heart or dyspnea, patients miss a key component of disease treatment.

Is anxiety a risk factor for a cardiac event? Based upon current knowledge, depression and anxiety disorders in association with chronic physical disorders often result in a cyclic downward spiral of a person's overall health. However, evidence concerning the sequence of developing physical and mental disorders is not well established. Scientists and clinicians often identify anxiety and depression as risk factors for cardiovascular disease when associated with unhealthy behaviors. Such behaviors include smoking, poor diet, sedentary lifestyle, and poor medication compliance.¹⁷ Resulting cardiac events due to poor lifestyle choices can further exacerbate a person's anxiety and/or depression as health deteriorates.

Depression and anxiety directly impact the pathophysiology of cardiorespiratory diseases leading to elevated cortisol levels (hyper-cortisolemia) and heightened sympathetic activity.¹⁷ Hypercortisolemia and enhanced platelet activity (associated with depression) lead to endothelial dysfunction and arterial plaque build-up, and stimulate a

chronic inflammatory response promoting the progression of atherosclerosis.¹⁷ Individuals with anxiety and depression demonstrate reduced heart-rate-variability (HRV) and impaired vagal tone, further adding to cardiovascular complications.¹⁷

Other complications with anxiety management in conjunction with CAD include the overlap of symptoms. Anxiety disorders can manifest as panic attacks marked by the abrupt surge of intense fear or discomfort that reaches a peak within minutes during which time four or more symptoms occur.¹⁸ Symptoms of panic attacks resemble symptoms associated with a myocardial infarction such as heart palpitations, chest pain, and shortness of breath, and can lead a patient to believe an a heart attack is evolving.¹⁸ The main difference is panic attacks will pass, leaving a person physically unharmed.

Independent of CAD, persons with a panic disorder are known to exhibit maladaptive behavior changes reducing subsequent panic attack risk such as avoiding physical exertion.¹⁶ With cardiopulmonary patients, avoidance behaviors are particularly disconcerting because such avoidance reduces the likelihood of a patient participating in rehabilitation programs.^{16,19}

Depression and anxiety are not always comorbid in response to chronic disease. Historically, more emphasis is placed on depression. Recently, investigators are studying the implications of anxiety alone in conjunction with chronic disease. Their findings demonstrate each element is a risk factor for the other. After a cardiac event, individuals are three times more likely to be diagnosed with anxiety.¹⁵ Note that anxiety attacks do not precipitate heart attacks. Nonetheless, anxiety disorders are associated with sudden cardiac death.²⁰ One hypothesis suggests sudden cardiac death risk is in part due to anxiety related to reductions in HRV. Reduced HRV negatively impacts autonomic tone and places an individual at higher risk for lethal ventricular arrhythmias.¹⁷

Several anxiety disorder treatments exist either with or without complications of chronic disease. The most promising treatments with the fewest side effects is exercise with information gaps existing for exercise therapy anxiolytic effects. Epidemiologic data are sparse, but accumulating evidence is promising as scientists propose potential physiologic mechanisms for exercise as an anxiolytic agent.¹⁶

Exercise as a non-pharmacological treatment

Scientific evidence supports using exercise for disease prevention and treatment of diseases including psychological conditions.^{2,21,22} In support of psychological benefits of an active lifestyle, healthcare professionals are gaining a better understanding of mental health improvements in diverse patient populations through exercise induced neuroplasticity.²³ Dunn et al. evaluated energy expenditures of 7.0 kcal/kg/week and 17.5 kcal/kg/week to determine whether exercise is an efficacious treatment for mild to moderate major depressive disorders (MDD).²¹ Their results demonstrate that an energy expenditure of 17.5 kcal/kg/week or equal to the exercise prescription guidelines established by the ACSM are effective in reducing MDD.^{21,24,25} Rately reviewed current scientific evidence regarding mental health and supports exercise as a means to improve mood status.²⁶

No current recommendations exist for an optimal exercise volume to elicit anxiolytic benefits. Wipfli et al. completed a meta-analysis of forty-nine randomized controlled trials and established an exercise threshold for achieving mood-altering exercise benefits.²⁷ The necessary exercise dose for optimal mental health was an energy expenditure of 12.5 kcal/kg/week. When exercise increased past 12.5 kcal/kg/week, the effect-size magnitude was decreased.²⁷ The duration of a single exercise session lies on a continuum with greater reductions in anxiety seen during longer exercise sessions (61–90 min) when compared to shorter sessions (1–30 min and 31–60 min).²⁷ While improvements in mood were observed for all exercise durations, a minimum duration was not proposed.

Wipfli et al. considered maximal oxygen consumption ($\dot{V}O_{2max}$) and

Table 1

Summary of human and animal studies evaluating a single exercise session and exercise as an intervention.

First Author (Ref #)	Subjects	Methods/ Measures/ Intervention	Results
Blumenthal et al., 1997 (20)	107 women and men coronary artery diseased patients documented during mental stress testing or ambulatory electrocardiographic monitoring	Subjects were randomly assigned to a 4-month program of exercise or stress management training Patients living at a distance from the facility formed a nonrandom, usual care control comparison group Myocardial ischemia was reassessed following a 4-month program of exercise or stress management training Patients were followed annually up to 5 years to document cardiac events, including death, nonfatal myocardial infarction, and cardiac revascularization procedures	22 patients suffered at least 1 cardiac event during a mean follow-up period of 38 months Stress management was associated with a relative risk of 0.26 compared with controls Relative risk for the exercise group was also lower than controls, but the effect was not statistically significant Stress management was associated with reduced ischemia induced by mental stress and ambulatory ischemia
Droste et al., 2003 (39)	Male mice	Exercise mice had access to running wheels and ran approximately 4 km per night for 4 weeks Sedentary control animals did not have access to running wheels for 4 weeks Plasma ACTH and corticosterone levels were measured In a second experiment, responses to stressful challenges to include novel environment exposure (mice were placed in new cages, containing clean sawdust, for 30 min), forced swimming, or restraint stress were evaluated Blood was collected immediately after a stressful challenge and plasma ACTH and corticosterone levels measured	Exercising mice's early-morning baseline plasma ACTH levels were decreased, whereas plasma corticosterone levels at the start of the dark phase were twice as high as control animals Forced swimming and restraint stress, exercising mice responded with higher corticosterone levels than those of the control animals but had similar ACTH levels Voluntary exercise results in complex, adaptive changes at various levels within the HPA axis as well as in sympatho-adrenomedullary and limbic/ neocortical afferent control mechanisms These changes represent the differential responsiveness of the HPA axis to physical and

(continued on next page)

Table 1 (continued)

First Author (Ref #)	Subjects	Methods/ Measures/ Intervention	Results
Dunn et al., 2005 (21)	80 adult women and men aged 20–45 years diagnosed with major depressive disorder	The primary outcome was the score on the 17-item HRSD ₁₇ . Four aerobic exercise treatment groups that varied total energy expenditure (7.0 kcal/kg/week or 17.5 kcal/kg/week) and frequency (3 days/week or 5 days/week) or exercise control (3 days/week flexibility exercise	emotional challenges 17.5 kcal/kg/week of energy expenditure group had significantly reduced HRSD ₁₇ scores at 12 weeks over lower energy expenditure of 7.0 kcal/kg/week or control groups No exercise frequency (3 day/week or 5 days/week) effect at 12 weeks
Ferris et al., 2007 (32)	15 physically active women and men	Subjects performed two 30 min bicycle ergometer rides at 20% below the ventilatory threshold and at 10% above ventilatory threshold BDNF and cognitive function were determined	BDNF values increased from baseline after the 10% above ventilatory threshold ride BDNF values did not change from baseline after the 20% below ventilatory threshold ride BDNF change did not correlate with $\dot{V}O_{2max}$ but BDNF did correlate with lactate change BDNF levels were significantly elevated in response to exercise, and the magnitude of increase was intensity dependent
Wipfli et al., 2008 (27)	49 randomized trials	Meta-analysis of randomized trials and dose-response	Exercise groups showed greater reductions in anxiety compared with groups receiving other forms of anxiety-reducing treatment These results provide Level 1, Grade A evidence for using exercise as a treatment for anxiety
Rasmussen et al., 2009 (35) (Human)	8 physically active men volunteers	Subjects completed a single exercise session of 4 h rowing at a work rate of 10–15% below lactate threshold Blood samples were collected from the radial artery and the internal jugular vein	BDNF release from the brain increased two- to three-fold above resting values during exercise At rest and during exercise, the brain contributed 70–80% of circulating BDNF and that contribution

Table 1 (continued)

First Author (Ref #)	Subjects	Methods/ Measures/ Intervention	Results
Rasmussen et al., 2009 (35) (Animal)	Forty mice divided into five groups of eight mice per group	One group of mice served as a control group and did not exercise The other mice exercised for 2 h on a treadmill (18 m min ⁻¹ at 10% slope) until exhaustion; then blood was collected either immediately after exercise, or after 2, 6 or 24 h of recovery	decreased following 1 h of recovery In mice, exercise induced a three- to fivefold increase in BDNF mRNA expression in the hippocampus and cortex, values peaked 2 h after exercise termination
LeBouthillier and Asmundson 2015 (28)	41 women and men volunteers (no indication of physical activity level given)	Subjects completed 30 min of aerobic exercise or a placebo stretching control Anxiety sensitivity, intolerance of uncertainty, and distress tolerance were measured at baseline, post-intervention and 3-day and 7-day follow-up <i>Measures</i> <i>Anxiety Sensitivity Index</i> - self-report measure of fear <i>Intolerance of Uncertainty Scale, Short Form</i> - 12-item measure of intolerance relating to uncertainty, ambiguity and the future <i>Distress Tolerance Scale</i> - a 15-item measure of tolerance of emotional distress	Subjects in the aerobic exercise group experienced significant reductions in all dimensions of anxiety sensitivity, but not the control group Intolerance of uncertainty and distress tolerance remained unchanged in exercise and control groups Data supports the efficacy of aerobic exercise in reducing anxiety in individuals and highlights the importance of using aerobic exercise to address specific mental health illnesses The exercise group has significantly reduced cortisol to the MIST Higher aerobic fitness had lower cortisol responses to the MIST MIST was inversely related to exercise-induced alpha-amylase and cortisol changes Higher bilateral hippocampus activity and lower prefrontal cortex activity were found in the exercise group
Zschucke et al., 2015 (42)		Subjects were randomized into either exercise on a treadmill at moderate intensity (60–70% $\dot{V}O_{2max}$) for 30 min, or performed 30 min low-intensity stretching and relaxation exercises Salivary cortisol and alpha-amylase were measured MIST and neural activations were assessed	

Abbreviations: ACTH = Adrenocorticotropic hormone, HPA Axis = hypothalamic-pituitary-adrenal axis, HRSD¹⁷ = 17-item Hamilton Rating Scale for Depression, MDD = major depressive disorder, BDNF = brain-derived neurotrophic factor, MIST = Montreal Imaging Stress Task, $\dot{V}O_{2max}$ = maximal oxygen consumption.

found given a low-intensity exercise dose, reductions in anxiety levels were achieved without significant $\dot{V}O_{2\max}$ improvements.²⁷ Mood improvements (i.e., reduction in anxiety levels) were independent of $\dot{V}O_{2\max}$ improvements. This finding is important as any population, regardless of initial fitness level, can experience improved mood benefits from exercise.²⁷ Such evidence further supports the necessity of dichotomizing anxiety and depression as outcome measures given the apparent differences in exercise dosage for advantageous psychological effects.^{21,27}

Future studies for better understanding the effects of exercise anxiolytic effects are needed. LeBouthillier and Asmundson conducted a randomized trial evaluating the anxiolytic effects of a single aerobic exercise session compared to stretching.²⁸ Aerobic exercise participation resulted in greater anxiety sensitivity reductions post-intervention when compared to stretching. These results support using exercise to ameliorate a pathologically heightened sense of anxiety.²⁸ Table 1 outlines the results of key studies (human and animal) referenced in this manuscript regarding the psychologic impact of exercise.

Consideration for future studies should also be given to the impact of menopause on women's psychological health regarding the anxiolytic exercise benefits.²⁹ Existing evidence support improvement in quantifiable measures of menopausal symptoms, cardiometabolic risk profile (i.e., lipid profile), and depression; but little analysis of change in anxiety levels is discussed.³⁰

Current hypotheses on the pathogenesis of anxiety and the effects of exercise

Studies concerning the exercise health benefits for anxiety do not provide a complete picture of the true prevalence of anxiety due to the common avoidance of social interaction and reduced willingness to engage in novel activities like research participation. Scientists face obstacles in studying mood disorders because efforts are hindered by the precise symptoms being studied. Also, incomplete understanding of biological mechanisms behind anxiety disorders exist. Scientists have developed several biological hypotheses attempting to better understand the etiology of anxiety.

Brain concentrations of serotonin – the serotonin hypothesis

The serotonin hypothesis is the most widely known and accepted hypothesis for explaining anxiety and depression.²⁷ Individuals with anxiety or depression possess lower brain serotonin concentrations. Therefore, a common pharmacological treatment uses selective serotonin reuptake inhibitors (SSRIs) to block the reuptake of serotonin by the pre-synaptic neuron. Increasing the concentration of serotonin in the synaptic cleft of brain neurons increases the likelihood of serotonin binding to receptors.²⁷

Exercise is believed to provide similar anxiolytic effects under the serotonin hypothesis. Instead of blocking the reuptake of serotonin by the pre-synaptic neuron, exercise elevates serotonin levels above sedentary baseline values.²⁷ Like pharmacological treatments (i.e., SSRIs), the elevated peripheral serotonin levels post-exercise suggests a positive association between exercise and anxiolytic effects.^{23,27}

Scientific investigations are limited to measuring central serotonin in animal models because direct serotonin measurements (brain serotonin concentrations) cannot be completed in living human participants. Fortunately, indirect measurements in humans through blood serotonin levels provides meaningful information.²⁷

Scientific investigations concerning exercise as an anxiety treatment are relatively new. No thresholds are established for exercise intensity or volume to elicit meaningful effects. Current data suggest an inverse relationship between duration of exercise and anxiety in individuals with clinical anxiety disorders.²⁷

Brain derived neurotrophic factor hypothesis

Brain Derived Neurotrophic Factor (BDNF) is a protein and growth factor influencing maintenance, growth, and neuron survival. The origin or expression of BDNF is not completely understood, but evidence supports the neurotrophin's role in memory, cognition, and anxiety disorders.³¹

Multiple studies using animal models provide crucial information because human brain BDNF concentrations from cortical mass cannot be directly assessed to determine association with anxiety-like behaviors. Animal studies demonstrate blood BDNF concentration is strongly correlated with brain BDNF concentration due to bidirectional transport across the blood brain barrier, allowing scientists to draw conclusions about central concentrations when only measures of peripheral concentrations are available in humans.^{31,32} Peripheral blood BDNF concentrations are used as non-invasive estimates of brain BDNF concentrations for anxiety disorders.²⁸

The mechanism for lower brain BDNF levels and the presence of anxiety is not well understood, but present studies observe reduced blood BDNF levels in patients with anxiety disorders.³³ Pharmacological treatments for anxiety disorders result in elevated blood BDNF concentrations. Such treatments include the use of anti-depressants, exercise, and a combination of both.³⁴ To understand the direct impact of BDNF levels in brain tissue, Rasmussen et al. evaluated brain BDNF and found mRNA increases following a single exercise session in laboratory rat, and also report increased hippocampal BDNF and brain BDNF mRNA following a single exercise session of either voluntary or forced running.³⁵

Rasmussen et al. also conducted a human trial utilizing 4 h of rowing.³⁵ Upper body exercise was chosen to focus on local production of BDNF from the working skeletal muscle with blood samples taken from the brachial artery. As a surrogate to analyzing the brain's contribution of BDNF production, blood samples obtained from the internal jugular vein were compared to samples from working skeletal muscle and at rest. Two hours into a 4-h exercise session, neither arterial nor venous BDNF blood samples differ from resting concentrations. At the conclusion of 4 h of exercise, brachial artery and internal jugular vein BDNF levels were significantly increased when compared to resting values. BDNF concentrations from the jugular vein (indicative of brain-tissue BDNF levels) were increased two- and threefold from rest. These findings provide two conclusions. First, the increase in the brain's contribution to circulating BDNF is likely due to the increase uptake of IGF-1 – precursor to BDNF. Second, a threshold for BDNF increase was established – an exercise-intensity with work rate averaging 160 ± 38 W for greater than 2 h was needed to elicit a significant effect.³⁵ Similar results were found by Ferris et al. who utilized ventilatory threshold as an intensity indicator.³² Though parameters for a minimal exercise-intensity were not determined, these data establish an exercise intensity-dependent association with serum BDNF in human participants.³² No information was found explaining the biological mechanism behind why increased blood BDNF levels are associated with exercise. Further research is needed regarding blood BDNF levels with exercise.

Endorphin hypothesis and hypothalamo-pituitary-adrenocortical axis hypothesis

Identification of the opioid receptor within neural tissue is, in part, responsible for the naming of the endogenous opioid system as is the identification of specific naturally produced peptides exhibiting opiate-like properties. The endogenous opioid group called endorphins is the best-known example, specifically referred to as the beta-endorphin system, and is of interest to scientists given the relationship with physical activity.³⁶

Cell bodies of the beta-endorphin system are found in two independently regulated anatomical systems. The first system involves the hypothalamus while also innervating parts of the brain stem and medulla

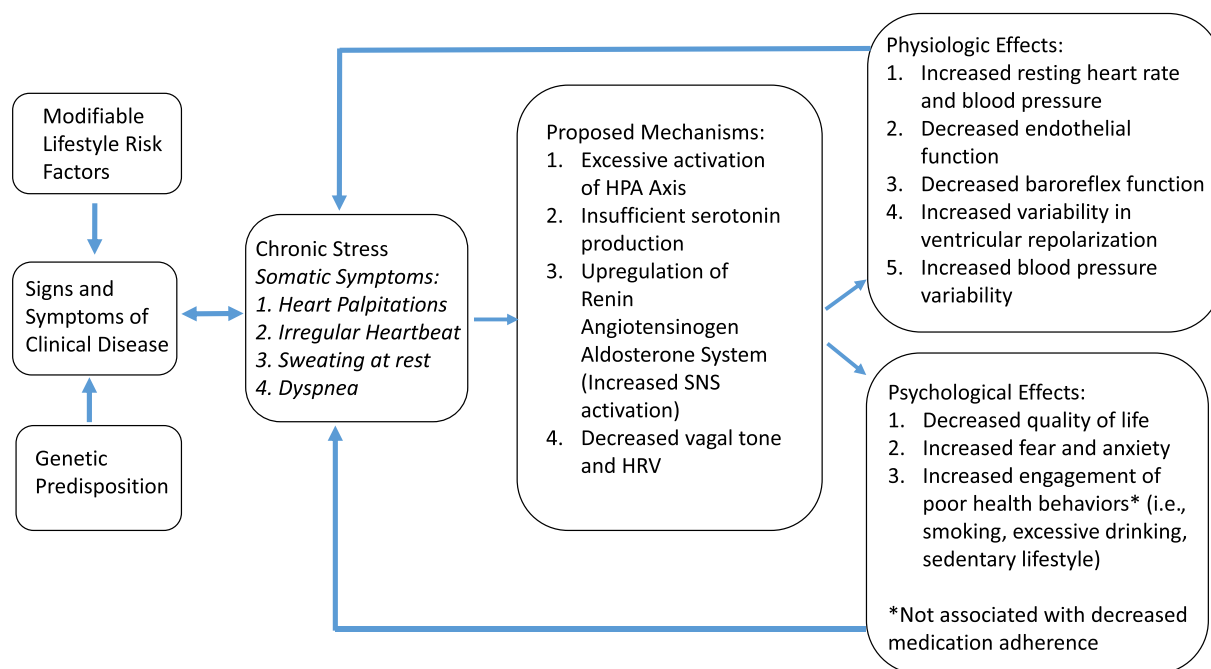


Fig. 2. Psychosocial Impact and Physiologic Effect of Chronic Stress.

The relationship between psychological and physiological effects of chronic stress create a positive feedback cycle leading to the development of anxiety and clinical manifestations of cardiovascular disease.

Abbreviations: HPA Axis = Hypothalamo-Pituitary-Adrenocortical Axis; RAAS = Renin Angiotensinogen Aldosterone System; SNS = Sympathetic Nervous System; HRV = Heart Rate Variability

The information for developing this figure comes from Mampuya. *Cardiovasc Diagn Ther.* 2012 (Reference 43) and Pacurari. *Int J Inflamm.* 2014 (Reference 44).

oblongata.³⁶ The second system begins with the anterior pituitary gland and the secretion of beta-endorphin and is closely associated with the release of adrenocorticotrophic hormone (ACTH). These two substances are secreted in response to physical stress. Because of equal representation of blood ACTH and beta-endorphin, present evidence suggests that post-exercise blood beta-endorphin concentrations are mostly due to anterior pituitary release.^{36,37}

Endorphins released into the bloodstream are taken up by opioid receptors present throughout the body causing heart rate reductions by sympathetic inhibition and parasympathetic activation.³⁸ Current evidence support that prolonged submaximal exercise increases the release of beta-endorphin which lowers post-exercise heart rate and blood pressure.³⁶ Because of delayed and residual effects of circulating plasma beta-endorphins, anxiety reductions are likely to elevate post-exercise beta-endorphins blood concentrations. The resulting lower heart rate supports the notion of lower anxiety levels in response to altered autonomic regulation.³⁶

Further studies regarding the endorphin hypothesis are needed to clarify and define possible confounding variables associated with this hypothesis. For example, because of the similarities in amino acid sequence existing between ACTH and beta-endorphin, the co-release of beta-endorphin with the parasympathetic release of ACTH can confound the accurate detection of beta-endorphin. Though ACTH is a neurotransmitter, ACTH is also a stress hormone released by pituitary gland during exercise. As ACTH's and beta-endorphin's structure are similar, determining individual physiological impact of each is difficult.³⁷ However, the main limitation to the endorphin or endocannabinoid hypothesis is that endorphins cannot cross the blood brain barrier, increasing the difficulty of studying and evaluating endorphins produced centrally in humans. The ability to study central endorphin production in animal models helps reduce the literature gap.³⁷

The hypothalamo-pituitary-adrenocortical axis (HPA) is a complex system mediating animal and human response to stress.^{39,40} Scientists

who reject the notion of the endorphin hypothesis find the HPA axis theory more plausible. Studies concerning HPA axis suggest that beta-endorphin is a collateral component of ACTH action and not a prime mediator. Among the most crucial components of the HPA axis is the regulation for the release of ACTH from the anterior pituitary gland, stimulating the release of glucocorticoid hormones, mainly cortisol, from the adrenal cortex. Along with the release of ACTH is the release of beta-endorphin as was discussed in the endorphin or endocannabinoid hypothesis.

Under HPA axis control, plasma stress hormone concentrations such as cortisol are increased. The body will release cortisol and will elevate sympathetic activation during exercise. HPA axis is activated when exercising, and this response is different from activation experienced during chronic distress. When exercise ends, stimulation of these systems ends and returns to pre-exercise conditions. Note, the body does not necessarily acclimate to greater stress levels. Instead, the physiological systems become more capable of re-establishing homeostasis.⁴¹ The body experiences reduced plasma cortisol concentrations after exercise training and during a single exercise session.⁴² These same results have also been shown in animal models where voluntary wheel running is related to neural activation of different regions in the brain.⁴¹ Therefore, improved mood status and reduced levels of anxiety are likely attributed to a better regulation of the HPA axis with the co-release of beta-endorphin playing a supporting role. The HPA axis hypothesis views exercise as a means of managing elevated stress levels often associated with chronic anxiety. Perhaps better addressed as co-dependent hypotheses, the endorphin hypothesis and HPA axis hypothesis support the use of exercise as a treatment even if the biologic mechanism is not completely understood.

Application to practice

Stress is a modifiable factor currently accounting for 30% of

attributable risk for myocardial infarction.⁴³ Fig. 2 illustrates the positive feedback loop between chronic stress, anxiety, and the development of clinical disease. Chronic stress compromises the optimal function of various biological processes (renin angiotensin aldosterone system) including those systems responsible for the homeostatic balance of cardiovascular and pulmonary function.⁴⁴ For all individuals but especially cardiac patients, managing stress is an important part of risk factor modification.

Cardiac rehabilitation programming often offers various stress management techniques. Utilization of stress management methods is beneficial for reducing the risk of subsequent cardiac events. Blumenthal et al. evaluated 170 CAD patients and found completion of stress management programming with exercise reduced the risk of a second myocardial infarction by 26%.²⁰ A comprehensive cardiac rehabilitation program should address the mental and physical aspects of chronic disease.

Conclusion

Though the etiology of anxiety is not completely understood, clinicians gain insight to a growing number of treatment options including the most potent medicine – exercise.² Evidence continues to grow in support of incorporating exercise as an integral treatment option. Particularly after diagnosis of CAD or COPD, including exercise as part of the medical management plan improves functional capacity, alleviates symptoms of anxiety, and improves quality of life.

Submission statement

The manuscript has not been published and is not under consideration for publication elsewhere.

Authors' contributions

AGS performed the literature review, created Figs. 1 and 2, participated in writing, and analyzes of data. JLD participated in writing, analyzes of data, and was responsible for the overall review. Each author contributed equally to the drafting and final manuscript.

Conflict of interest

The authors have no conflict of interest to report.

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