BIOFEEDBACK ASSISTED STRESS MANAGEMENT TRAINING IN PATIENTS WITH CORONARY ARTERY DISEASE

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BIOFEEDBACK ASSISTED STRESS MANAGEMENT TRAINING IN PATIENTS WITH CORONARY ARTERY DISEASE

GREGORY JAMES BOLWELL

ABSTRACT

Heart disease is the leading cause of death in the United States for both men and women, and coronary artery disease (CAD) is the most common type of heart disease, often leading to heart attacks. Over a long period of time, CAD can weaken the heart muscle, causing heart failure and arrhythmias. Three well established events which occur in CAD are an over activation of the sympathetic nervous system, increased inflammation and psychological distress.

Biofeedback assisted stress management (BFSM) is a form of stress management that allows one to see how their physiology changes, in real time, as they either become stressed or relaxed. The patient is coached by the biofeedback therapist on strategies for reducing stress while the patient can see how effective the strategies are by looking at a computer screen in front of them. We hypothesized that in patients with CAD, BFSM training could help positively affect an over activation of the sympathetic nervous system, increased inflammation and psychological distress.

To test this hypothesis, 19 patients enrolled in the cardiac rehabilitation program at the Cleveland Clinic were separated into a biofeedback group (BF) and a usual care (UC) group. All 19 enrolled patients underwent a stress assessment in which they were tested for blood markers of sympathetic activity and inflammation and underwent a mental stress test. Both the BF and UC patients received their normal cardiac rehabilitation but the BF patients also received 8 weekly sessions of BFSM. After the 8 weekly sessions of BFSM were complete, the patients had a second stress assessment in
which they had their blood tested for the same markers as the first stress assessment and also underwent the same mental stress test.

We found that the BFSM was effective in teaching CAD patients to breathe at a lower rate, but saw little difference between the BF and UC groups in regards to other physiological markers of stress. We also saw little difference between the BF and UC groups in regard to the markers of sympathetic activity and inflammation. This suggests that further research is needed to test the efficacy of BFSM in patients with CAD.
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CHAPTER I
INTRODUCTION

Biofeedback is a form of training in which patients are taught to regulate their own physiology. The uniqueness of biofeedback in working towards this goal is that patients are able to see their own physiological output on a computer screen with immediate feedback (Frank, Khorshid, Kiffer, et al. 2008). The immediate feedback is a form of operant conditioning because it rewards patients when they successfully improve their physiology and illustrates to the patient when his or her physiology worsens (Moravec, McKee, 2011). This allows patients to know exactly what is causing them to improve their physiology, exactly when their physiology is changing and the magnitude of their physiological change. Biofeedback can be used in a wide range of situations, from a treatment for different health conditions to enhancing an athlete’s performance on the athletic field. For the purposes of this study, biofeedback will be used mainly as a stress management tool for patients with coronary artery disease (CAD).

1.1 Coronary Artery Disease
Heart disease is the leading cause of death in the United States for both men and women, and CAD is the most common type of heart disease, often leading to heart attacks (Rosamond, Flegal, Friday, 2007). CAD occurs when plaque builds up on the walls of the coronary arteries, restricting blood flow to the heart. This buildup is called atherosclerosis (Ross, 1999). When the plaque builds to a magnitude where there may be complete obstruction of oxygen-rich blood flow to the heart, it causes a heart attack. Most people may not know they have CAD until the heart attack occurs, which unfortunately for a number of people, is too late. Further, over a long period of time, CAD can weaken the heart muscle, causing heart failure and arrhythmias (Hansson, 2005). Heart failure occurs when the heart is too weak to adequately pump blood through one’s body and arrhythmias are changes in the normal beating pattern of the heart. Numerous studies of CAD have indicated an association between inflammation and CAD (Hansson, 2005), and patients with CAD have been shown to have an over activation of the inflammatory reflex (Ross, 1999). The body recognizes when the heart has CAD and initiates the inflammatory reflex. However, doing so actually causes more harm because the inflammation further decreases cardiac function.

There are several markers for inflammation, which are elevated in patients with CAD (Safranow, Dziedziejko, Rzeuski, et al. 2009), including tumor necrosis factor alpha (TNF-alpha), myeloperoxidase (MPO) and C-reactive protein (CRP). TNF-alpha may participate in the pathophysiology of CAD, and it has been shown to be a reliable predictor of CAD (Chu, Yang, Mi, et al. 2012). MPO is a proinflammatory enzyme that is elevated in ruptured plaque and can be measured in the bloodstream. MPO catalyzes the conversion of chloride and hydrogen peroxide to hypochlorite and it is secreted during
inflammatory conditions (Loria, Dato, Graziani, et al. 2008). Similar to TNF-alpha and MPO, CRP is a marker of inflammation. Moderately elevated levels of CRP are an independent risk factor for CAD in a healthy population (Hansson 2005). All three of these inflammatory markers are associated with CAD and can be measured in the blood.

Along with the physical symptoms that come with CAD, CAD also causes psychological distress (Moravec, 2008). Those with CAD have to constantly be aware of their disease and how it affects their daily life; as they must watch their diet, exercise as often as they can and attempt to limit their stress. This can create a stressful situation because one knows the consequences if one fails to properly maintain a healthy lifestyle. Such stress, along with the physical limitations of CAD, can cause a lower quality of life (Brotman, Sherita, Wittstein, 2007). Along with a lower quality of life, it has been found that anxiety is highly prevalent in patients with CAD; between 28-44% of younger patients and 14-24% of older patients with CAD have been shown to be anxious (Zafar, Yepes, Shimbo, 2010). Such high prevalence of anxiety is concerning, when considering anxiety is a frequently encountered comorbidity of depression (Kessler, Chiu, Demler, et al. 2005).

Depression has also been found to be associated with CAD. Not only has it been found that CAD can cause depression, but depression is an independent risk factor for CAD and complications associated with CAD. Further, depression contributes to an unhealthy lifestyle and poor compliance with treatment (Khawaha Westermeyer, Gajwani, 2009). When considering the high prevalence of psychological issues associated with CAD, and the severely negative effects they have on disease and disease progression, it is evident that treating patients with CAD for quality of life, stress,
depression and anxiety is vital to keeping them healthy. It may not be possible to eliminate psychological distress in such patients, but the importance of treating the psychological issues and attempting to minimize their effects should be made a priority. High levels of stress and anxiety are associated with an over-activation of the sympathetic nervous system. When the sympathetic nervous system is activated, it releases neurotransmitters into the body. Markers of sympathetic activity, such as epinephrine (EPI), norepinephrine (NE) and dopamine can be found in the blood. Therefore, one can test for biomarkers of stress and anxiety by examining levels of EPI, NE and dopamine in the blood.

1.2 Biofeedback Assisted Stress Management

While biofeedback can be used as a form of operant conditioning, it can also be used in tandem with stress management (Lehrer, Woolfolk, Sime, 2007). This is possible because stress, both chronic and acute, is mediated through the autonomic nervous system, and biofeedback helps people control autonomic activation. Specifically, when biofeedback is used as a form of stress management, the goal is to decrease sympathetic nervous system input, allowing the parasympathetic nervous system to become more involved in regulating physiologic functions. When biofeedback is used in this manner, as a stress management tool, it is referred to as biofeedback assisted stress management (BFSM).

BFSM is a technique in which sensors that detect physiological markers of stress (respiration rate, heart rate, perspiration, finger temperature etc.) are placed on individuals and they are able to see how their stress physiology changes when put in
different mental situations (McKee, 2008). In this way, the use of biofeedback is a tool for stress management training. The patient will use the feedback from the sensors along with their stress management training to help change their physiology; this combination of biofeedback used in conjunction with stress management is what creates BFSM. BFSM requires a trained biofeedback therapist who not only teaches the patient about their physiology, but also provides the patient with multiple stress management techniques; such as guided imagery or progressive muscle relaxation. The therapist must be knowledgeable in both the biofeedback as well as the stress management aspect of BFSM for the training to be successful. Further, in order for BFSM to be successful, the patient must be able to mentally change their thoughts, as well as their respiration rate. Therefore, the patient must learn several stress management strategies, with the biofeedback being used as a reinforcement to display how effective the training may be. Thus, the success of BFSM relies more on the patient than it does on the therapist. The patient must be willing to take instruction from the therapist and attempt as best they can to make changes in their thought process according to what the therapist coaches them to do. Such a combination of factors in this type of stress management (BFSM) can be complicated to learn and it is necessary to have multiple training sessions before the patient can become fully able to apply the training to their daily life.

As stated, in order for BFSM to be successful the patient must be able to see and understand how their physiology changes during each session. In order to achieve this goal the patient must have a screen which displays their physiology and how it changes in real time, as the session unfolds. Typically, the patient has their own screen which may display one or two aspects of their physiology at a time, which allows the patient to focus
their attention on that specific area of their physiology. The biofeedback therapist however, typically has a screen of his/her own which displays the output from all of the sensors at once. The therapist uses this screen to help follow the patient’s progress as a whole throughout the training session. The therapist will be able to switch the patient screen from one type of physiological output to another at any moment they desire. Thus, while practicing a specific stress management technique, if the patient is excelling in regards to improving one aspect of their physiology, the therapist is able to change the patient screen to that output immediately, so the patient can see his/her progress. Typically, the physiological aspects which are easiest to improve with simple stress management techniques, such as respiration rate, are focused on first. Once the easier aspects of physiology are shown to be successfully manipulated by the stress management, the therapist will move on to more difficult forms, such as heart rate variability (McKee, Moravec, 2010).

Further, in order for BFSM training to be successful, the therapist must teach the patient a wide variety of stress management techniques. These strategies range from simple ways to relax for a few minutes such as guided imagery and progressive muscle relaxation, to new strategies for a healthier outlook toward daily life using mindfulness or cue controlled relaxation (Moravec, McKee, 2011). The purpose is to provide the patients with a number of different stress management strategies which they can use on their own, as well as practice during the training sessions, to see how effective they are in different situations. When the patients finish all of their training, they should be equipped with multiple techniques to better manage their stress. These strategies are used in conjunction with the biofeedback equipment so the patient can have reinforcement for how effective
the different stress management techniques may be. The most important aspect of BFSM is for the patient to learn to successfully manage their stress on their own. While it is helpful for the patient to have a weekly stress management session, for optimal benefit the patient must be able to take what they learned in the training sessions and apply such information to their daily lives. Therefore, when the patient is away from their therapist and biofeedback equipment, and they are faced with a sudden stressful situation, they will be able to keep themselves calm using the techniques they have mastered through BFSM.

1.3 Heart Rate Variability

An important aspect of BFSM is teaching the patient to regulate their autonomic nervous system, and recently heart rate variability (HRV) has been used as a parameter to measure autonomic balance and cardiac resilience. Simply put, HRV is a measure of the beat-to-beat fluctuations in heart rate. In order to adapt to different situations at a moments notice, the heart must be able to increase or decrease its beating almost instantaneously. Therefore, a healthy heart will have high fluctuation in its beat-to-beat heart rate, and a high HRV. A weakened heart will be unable to adequately fluctuate and therefore will have a low HRV (Lehrer, Woolfolk, Sime, 2007). It has been shown that decreased HRV is associated with a variety of diseases which affect autonomic nervous system dysfunction, stress and depression (Kleiger, Miller, Biggar, 1987).

In order to measure HRV, one begins with an analysis of R waves on an electrocardiogram (EKG). While one measures heart rate by examining the number of R waves per minute, HRV is measured using the amount of time in between successive R waves; referred to as the inter-beat interval (IBI). Therefore, two people with the same
heart rate over a 5 minute span may have very different HRV, depending on their IBI. A healthy heart will have variable IBI’s within a 5 minute span, indicating a high HRV. An unhealthy heart, however, will not be able to show variability in its function and will have a low HRV.

1.4 Physiological Markers of Stress

Physiological markers of stress include, but are not limited to respiration rate, heart rate, perspiration and finger temperature. Respiration rate is most easily controlled, as one can consciously focus on their breathing and choose to breathe faster or slower, on command. Typically, when a person breathes at a rate of 6 +/-1 breaths per minute they will achieve a relaxed state of breathing. However, people may have certain medical conditions which don’t allow them to breath at such a low rate; in these cases that patient is asked to breathe at the lowest rate which is comfortable for him/her. Heart rate is also a marker of stress, as one will typically have an elevated heart rate when feeling stress. The heart will beat faster and have an increase in force of contraction in an attempt to pump blood to the large muscles in the body. Skin conductance refers to the skin’s ability to conduct electricity. When stressed, sweat is secreted from the palms and fingers, and the more sweat released allows the skin to conduct more electricity. Therefore, as one becomes more stressed, they will have sweatier hands and fingers, which in turn allows the skin to conduct more electricity. Finally, finger temperature is a marker of stress as one’s finger temperature will decrease upon feeling stress. Upon sympathetic arousal, vasoconstriction occurs in the fingers and toes, which reduces the blood flow to these areas. In turn, the reduced blood flow causes the finger temperature to decrease.
1.5 BFSM and the Autonomic Nervous System

BFSM may be particularly useful in patient populations in which the patient’s disease causes an imbalance in the autonomic nervous system. An increase in sympathetic activity and decrease in parasympathetic activity is common in many chronic diseases (Brotman, Golden, Wittstein, 2007). As noted, BFSM helps relieve stress and helps one learn to manage one’s reaction to stressful situations. In turn, this will help activate parasympathetic activity and minimize over activation of the sympathetic nervous system. It has been demonstrated that increasing the parasympathetic nervous system and decreasing the sympathetic nervous system can subdue the inflammatory reflex (Tracey, 2002). Tracey (2002) also indicated that morbidity and a shortened life span are symptoms of an excess in the inflammatory response. Unfortunately, an increase in inflammation is also a component of many diseases. Therefore, patients with a disease that causes an over activation of the inflammatory reflex may benefit from BFSM because they will learn to better regulate their autonomic nervous system and in turn reduce the activation of the inflammatory reflex. However, this is not easily achieved as most people do not how to regulate their autonomic nervous system, and many chronic diseases are accompanied by stress related to the disease, which only increases sympathetic nervous system activity.

1.6 Physiologic Testing

For BFSM to be considered successful, the patient must be able to take the techniques they learned and apply them to their own stressful life situations. However, it is nearly impossible to test whether someone is able to do this in a natural setting, as
often one does not know when they will be faced with stress. Therefore, in order to help measure the success of BFSM it is not uncommon to have a pre and post physiological test in which the patient is put through a series of stressful situations in a laboratory setting before and after they receive BFSM. Patients will be hooked up to the BFSM sensors and then put through a series of stressful situations, during which their stress responses will be recorded. If one shows an improvement in their stress response or an ability to recover more quickly to their baseline physiological levels on the post test, it will demonstrate that the BFSM was successful in helping the patient manage their stress.

1.7 BFSM and CAD

Along with current treatments for CAD, BFSM may be a useful addition to help prevent disease progression. It has been shown that just as the nervous system controls heart rate and other vital functions, it also controls the inflammatory response in real time (Tracy, 2002). Therefore, if someone with CAD can use BFSM to help manage their stress, and regulate their own autonomic nervous system, they should also be reducing their inflammatory reflex (Rozanski, Blumenthal, Davidson, 2005). This may help prevent someone with CAD from having further disease progression.

As stated, HRV is an indicator of heart function, and if one can improve their heart rate variability, they will improve the condition of their heart. Patients with CAD have been shown to have decreased HRV (Del Pozo, Gevirtz, Scher, 2004), which in turn has been associated with increased severity of CAD. However, BFSM has been shown to improve heart function, by improving HRV in patients with CAD (Del Pozo, Gevirtz,
Scher, 2004). In doing so, improving the HRV in patients with CAD positively affects disease progression.

Stress management has been shown to reduce depression and anxiety, as well markers of disease progression in patients with CAD. One study found that CAD patients who received stress management had lower blood pressure, heart rate, cholesterol and psychologic distress than those in the control group (Linden, Stossel, Maurice, 1996). A further study demonstrated that stress management in patients with CAD reduced distress and improved cardiovascular biomarkers of risk, including HRV and mental stress induced ischemia (Blumenthal, Sherwood, Babyak, 2005). Using the evidence from these studies, one can conclude that BFSM could be a useful tool in cardiac rehabilitation.

1.8 Summary and Hypothesis

As previously stated, (1) CAD is a disease that affects a large number of Americans, and has symptoms which include inflammation and psychological distress. (2) BFSM is a tool that can be used to help patients manage their stress and regulate their own physiology. (3) HRV is a measure of autonomic balance and cardiac resilience which can be used to show one’s ability to regulate their own physiology. (4) Physiological testing before and after BFSM can help demonstrate whether BFSM was able to help one regulate their physiology. (5) BFSM may be particularly useful in patients with CAD because two symptoms of this disease are dysfunction of the autonomic system and inflammation.

We hypothesized that BFSM, by interfering with over-activation of the sympathetic nervous system and augmenting activity of the parasympathetic
nervous system, will have a significant impact on symptoms including inflammation and health related quality of life in patients with CAD. We are also testing the hypothesis that the intervention will teach patients with CAD to better manage their stress, through control of their own physiology.
CHAPTER II
METHODS

2.1 Study Design

The study was a randomized clinical trial of biofeedback assisted stress management (BFSM) in patients with established coronary artery disease. Patients were randomized 1:1 to the intervention vs usual care. Our hypothesis was that BFSM in the intervention group would improve autonomic nervous system balance, health-related quality of life, anxiety, depression, life engagement, and biomarkers of autonomic activation and inflammation.

A total of 19 patients attending cardiac rehabilitation at the Cleveland Clinic were recruited for the study. Coronary artery disease was established by history of a myocardial infarction, percutaneous intervention or coronary artery bypass surgery. All patients attended a first session in which they underwent an assessment of their physiological response to mental stress, a blood draw, and filled out questionnaires related to health-related quality of life, life engagement, anxiety and depression. After the first session, those in the usual care group were not seen for nine weeks, after which they participated in the same assessment as they completed at the first visit. Following the first
session, those randomized into the intervention group had eight weekly sessions of BFSM with a certified biofeedback therapist. After the eight weeks of BFSM, patients in the intervention group also participated in the same stress assessment as they completed at the first visit.

Data from the first assessment were compared to those from the second assessment visit in both groups of patients. This comparison allowed us to test the hypothesis that BFSM had an effect in the patients who received the intervention vs the usual care group. We structured the BFSM training sessions for the patients to have one session every week, on average, giving them time between sessions to practice what they had learned at home. For that reason, at the completion of each session, the patients received a homework packet which they were asked to fill out and return at the beginning of the next session. Structuring the training sessions this way also allowed the patients to learn a new stress reduction technique each week, and then attempt to implement the new techniques in their daily lives. The overall study design is shown in Figure 1.

2.2 Patient Selection

In order to participate in the study, patients were required to be enrolled in the cardiac rehabilitation program at the Cleveland Clinic. Upon entering the cardiac rehabilitation program, all patients who met inclusion criteria for the study were informed of the research by Dr. Gordon Blackburn, who is the exercise physiologist in charge of the cardiac rehabilitation program at the Cleveland Clinic. Inclusion criteria were: fluency in English, mental capacity sufficient to understand the basics of the study, age between 18 and 90, and the ability to speak and hear English. If questionable, adequacy
Figure 1. Overall study design.
of mental ability was determined by a health psychologist familiar with the study. Patients were excluded if they had a pacemaker or an internal defibrillator; due to concern about interference with study equipment. Patients who were willing to participate were consented by Dr. Blackburn, using IRB-approved protocols. Once the patient signed the consent form, a study assistant retrieved the form from Dr. Blackburn and called the patient to schedule the first study session. All patients who chose to enroll participated in their normal cardiac rehabilitation treatment, along with the study. In total, 19 cardiac rehabilitation patients were enrolled in the study. The patients were randomized 1:1 into the intervention group and the usual care group, upon completion of the first study visit.

2.3 Patient Assessment

The patient assessment occurred in sessions 1 and 10. Once consented, the patients were contacted by phone to schedule the first session (session 1). Upon arriving at the first session, the patient was greeted by a study assistant and asked to rest lying down and relax as well as they could in a private patient room, for thirty minutes. It has been demonstrated that resting horizontally for thirty minutes will bring blood markers of sympathetic and parasympathetic activity to an individual’s baseline level (Sala, Santin, Rescaldani, et al. 2006). Taking the patients to their baseline level would help rule out the possibility of a stressful event from earlier in the day affecting their markers of sympathetic activity and inflammation. After the thirty minute rest period, a nurse was brought into the patient’s room and drew blood into six 4ml tubes. Directly after all six tubes were filled, a study assistant put them in an ice cooler and transported them to the Clinical Research Unit analytic lab at the Cleveland Clinic, where epinephrine (EPI),
norepinephrine (NE) and dopamine were measured as markers of sympathetic activity. Other measures included c-reactive protein (CRP), myeloperoxidase (MPO) and tumor necrosis factor alpha (TNF-a), which are markers of inflammation. This process of drawing the blood was performed in the exact same way during sessions 1 and 10; allowing us to compare the baseline biomarker levels of the patients in the usual care group to those in the intervention group between session 1 and session 10.

After the blood draw in both sessions 1 and 10, patients in the intervention group and the usual care group were asked to fill out four questionnaires. The questionnaires included: the life engagement test (LET), the patient health questionnaire 8 (PHQ-8), generalized anxiety disorder scale 7 (GAD-7), and the short form (36) health survey (SF-36). The LET is designed to measure purpose in life, defined in terms of the extent to which a person engages in activities that are personally valued (Scheier, Wrosch, Baum, et al. 2006). The PHQ-8 is an 8 question diagnostic and severity measure for depressive disorders (Kroenke, Strine, Spitzer, et al. 2009). The GAD-7 is a brief measure of symptoms of anxiety, based on diagnostic criteria described in DSM-IV (Kertz, Bigda-Peyton, Bjorgvinsson 2012). The SF-36 is a 36 item questionnaire that yields an 8-scale health profile as well as summary measures of health-related quality of life (Walters, Munro, Brazier 2001). The results of the SF-36 are separated into a physical component and a mental component. These four questionnaires were chosen because together they examined anxiety, mental distress and depression. They also indicated the overall mental health of each patient by examining not only their physical condition, but also how they view their own health and what effects, if any, their health condition has on their daily lives.
Once the questionnaires were completed, the study assistant connected the biofeedback equipment to the patient and explained how the equipment works. The equipment was the ProComp Infiniti from Thought Technologies (Montreal, QC). The ProComp Infiniti equipment included a respiration belt which measured how many breaths per minute the patient was taking, sensors which were placed on the patient’s forearms and recorded EKG, a temperature sensor which was taped around the patient’s smallest finger, as well as sensors which were placed on the patient’s ring and index fingers indicated the quantity of moisture on the patient’s skin reflecting sweat gland activity (referred to in the biofeedback literature as skin conductance).

Once the patient was connected to the biofeedback equipment and understood what would be happening during the study, the study assistant administered a 20 minute psychophysiologic stress assessment. The assessment began with a two minute baseline period during which the study assistant verified that all of the sensors were working and giving accurate feedback. Next, there was a five minute period during which patients were asked to close their eyes and relax as best they could. Following the self relaxation period, patients completed either the serial sevens test or the Stroop color words test; which test was administered first had been decided randomly prior to the session. The stress test lasted for 90 seconds and upon completion, patients were asked to once again close their eyes and relax as best they could for 5 minutes. After this self relaxation period, patients completed either the serial sevens or the Stroop color words test (whichever one they had not done initially). This stress test also lasted for 90 seconds. Finally, upon completion, patients were asked to close their eyes and relax as best they could for 5 minutes. Once this five minute period was completed, the stress assessment
was over and the equipment was disconnected from the patient. The stress assessment was structured in this way for three reasons: 1) to determine how well the patient is able to relax on his/her own without experiencing a stressor, 2) to measure the physiological response to mental stress, and 3) to measure how quickly the patient recovers from the stress response, if present. Data from the first five minute self relaxation showed how well the patient could relax on his/her own, any physiological changes during the Stroop and serial sevens tests showed how the patient reacted to stress physiologically, and the two five minute self relaxation periods after the Stroop and serial sevens tests measured the recovery from mental stress. The layout of the stress assessment is shown in Figure 2. After the stress assessment in session 1, the patients were randomized into the usual care group or the intervention group.

The outcomes from the physiological stress assessment were determined using the biofeedback sensors. Each sensor was used to detect a separate marker of physiologic stress. Respiration rate, heart rate, finger temperature, and skin conductance are all influenced by the autonomic nervous system. Some of these markers are more sensitive to stress than others, but it has been shown that all of these markers are indicators of stress (Moravec, CS, McKee MG 2011). Figure 3 shows the four sensors that were used to monitor the patient’s physiology. To measure respiration rate, the respiration belt is placed around the patient’s abdomen, just above the navel. The belt is sensitive to stretch and as the patient inhales and exhales, the respiration belt will expand and contract. It is the expansion and contraction of the belt which is projected in wave form as well as numerically, in breaths per minute. Generally, as the individual feels an increase in stress, respiration becomes faster and depth of breathing is reduced. Relaxed breathing is
Figure 2. Time distribution of the stress assessment
Figure 3. Biofeedback Sensors.

A) respiration belt, B) EKG sensor C) thermistor D) skin conductance sensor.
abdominal rather than thoracic, so placement of the belt around the abdomen records the correct type of breathing.

EKG electrodes were used to measure heart rate. When one becomes stressed, heart rate increases. EKG sensors are electrocardiograph sensors or pre-amplifiers, for directly measuring the heart’s electrical activity. The electrode amplifies the small electrical voltage that is generated by the heart muscle when it contracts. In turn, this signal was converted into a digital signal on the monitor, reflecting heart rate. For our study, we had three electrodes which were placed on the patient’s forearms.

Digital peripheral temperature was measured using a thermistor which was taped around the patient’s smallest finger using Millipore medical tape. Any changes in finger temperature were converted into an electrical current and displayed on the computer (in degrees Fahrenheit). As one becomes stressed, peripheral blood vessels constrict, and, in turn, there will be less blood flowing through the extremities. This results in reduced finger temperature.

Skin conductance, measured as the patient’s ability to conduct electricity between two sensors, was measured using silver-silver chloride electrodes which were put on the patient’s ring and index fingers using Velcro. As the moisture on the patient’s fingers increased, more electricity flowed between the electrodes. This conductance was recorded in micro Siemens and displayed on the computer. As the individual feels more stress, he/she begins to sweat and a higher skin conductance is measured.

2.4 Intervention (BFSM)
Patients in the intervention group participated in the BFSM. The goal of the training sessions was to acclimate the patients to the biofeedback equipment, explain to them what BFSM is, and teach them a variety of stress management techniques. In order to achieve this goal, we arranged the 8 training sessions such that patients would learn BFSM most efficiently. In the first and second training sessions, the patient was taught how the equipment works and how the human body reacts to stress, particularly with regard to the autonomic nervous system, and how to breathe abdominally. Once these two introductory sessions were complete, the purpose of the third training session was to find the patient’s ideal respiration rate. Every person has a certain optimal respiration rate where their heart and lungs function most efficiently (Sakakibara, Hayano, Oikawa, et al. 2013). Most people’s ideal respiration rate is 6 breaths per minute +/-2. Once the respiration rate was determined, the patient was asked to breathe at that rate for the remainder of the training sessions. The patient was also asked to breathe at that rate when they spent time practicing at home. For the remainder of the training sessions, patients were taught a different stress relaxation technique each session. After each session, the patient was asked to practice the new technique at home during that week. The sessions progressed in this manner for the remainder of the training sessions. The goal was to teach the patients a variety of stress relaxation techniques which they could then practice on their own and decide which ones worked best for themselves. Therefore, the patients would be able to take what they learned in the training sessions and apply the techniques to real life situations.

During intervention, the patient was hooked up to the biofeedback equipment for the entirety of the sessions. This allowed them to see how their physiology changed
throughout the course of the session. The patient was able to see their physiology changing, in real time, on a computer screen which was placed in front of them. In this manor, the biofeedback therapist could use the data from the patient’s physiology to help coach them throughout the sessions and highlight to the patient which stress management techniques were beneficial and which ones did not work as well for him/her. In order to make it easy for the patient to understand how the different indicators of physiological change fluctuated throughout the session, we programmed the software to include a different display screen for each of the physiological measures. Examples of some of the training screens are shown in Figure 4 (respiration rate), Figure 5 (finger temperature) and Figure 6 (skin conductance). This allowed the patient to focus on one aspect of their physiology at a time, without being bombarded with information. There were two screens which were more advanced and had the information from multiple markers of physiological activity, as shown in Figure 7, but these were only used in the later training sessions, when the patients were more advanced. The therapist had a separate computer which displayed all of the physiologic output on a single screen (Figure 8). It was important that in each training session the patients learned a new aspect of stress management, and that what they had learned was reinforced by the changes they saw in their physiology.

Another goal of the intervention was for the patients to take what they had learned about stress management and apply it to their daily lives. In order to achieve this goal, patients in the intervention group were asked to complete weekly homework packets in between session 2-10. In order to obtain routine home practice, the patients were asked to relax for a period of at least 10 minutes on their own each day, and practice the stress
Figure 4. Respiration Rate Patient Training Screen.
Let the lightbulb glow warmly by increasing finger temperature...

Temperature 92.23

Figure 5. Digital Peripheral Temperature Patient Training Screen.
Figure 6. Skin conductance Patient Training Screen.
Move heart activity into the **GREEN** range by breathing slowly and deeply and visualizing positive emotions.

![Heart Rate Variability Patient Training Screen](image)

**Figure 7.** Heart Rate Variability Patient Training Screen.
Figure 8. Biofeedback Therapist / Technician Screen.
management techniques which were taught in that week’s session. They were given a hand held thermometer which they were able to tape to their smallest finger during relaxation practice to record their finger temperature. The patients were also given a packet of homework sheets which asked them to rate on a 0-10 scale their level of stress before and after their practice, which relaxation technique they used, their finger temperature before and after their relaxation practice, their overall stress and overall pain levels for the day (rated on a 0-10 scale), as well as any comments regarding any special events, problems or successes they experienced during the day. The patients were asked to fill out one homework sheet every day during the study. This allowed both the patient and the therapist to track their progress at home, and made it easy for the patient to pinpoint which stress management techniques worked best for them.

2.5 Data Analysis

Data analysis incorporated four main questions: First, did intervention change one’s ability to increase markers of parasympathetic activity and decrease markers of sympathetic activity? This will be measured using the data from the physiological sensors during the 5 minute self relaxation periods at the beginning of each stress assessment. Second, did intervention change the way one reacts to stress or how quickly one can recover from stress? This will be measured using the data from the stress assessments. Specifically, the stressors and the self relaxation directly following the stressors. Third, did intervention change mental health or health related quality of life? This will be measured using the 4 questionnaires from the first and second stress assessments. Fourth,
did intervention change inflammatory markers and markers of autonomic nervous system activation? This will be measured using the results from the blood draw at the first and second stress assessments.

A within subjects t-test will be used to examine data all of the data from the first stress assessment. This will be done to see if there was any difference in the BF and UC group when they entered the study. In order to reduce a practice effect during the stressors in stress assessment one and stress assessment two, the stressors in stress assessment one will be averaged, as will the recovery periods. This will also be done in stress assessment two. Therefore, a mixed model repeated measures ANOVA will be used to examine the physiology. In any instances where the sphericity assumptions are not met a Greenhouse-Geisser transformation of the \( df \) will be used. Post hoc testing will be done using a series of pairwise comparisons, which use t-statistics. For the blood data and the questionnaire data, a repeated measures ANOVA will measure the data from stress assessment one to stress assessment two.
CHAPTER III

RESULTS

3.1 Patient Demographics

There were 19 total patients who participated in the study. One patient (ID# 15) withdrew from the study after being consented, but before completion of the first stress assessment. The patients in the UC and BF groups had a similar average age, both groups had more males than females, and relatively equal race distribution. This demographic data is shown in Table I. Individually, when the patients arrived for the first stress assessment, 17 patients were on a beta-blocker, 9 were using an ACE-Inhibitor, 5 patients were taking an AII-receptor blocker and 3 were on a calcium channel blocker. The drug distribution was also about the same in the UC and BF groups, as the individual patient demographics are shown in Table II.

3.2 Stress Assessment 1: Physiological Data (Table III)

Respiration Rate

In regard to respiration rate, when the patients attempted their first self relaxation
Table I. Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>BF</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 ± 12</td>
<td>60 ± 23</td>
</tr>
<tr>
<td>Sex</td>
<td>6 Male / 3 Female</td>
<td>9 Male / 1 Female</td>
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<tr>
<td>Race</td>
<td>5 White / 4 Black</td>
<td>5 White / 5 Black</td>
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<tr>
<td>Medications</td>
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<td>ACE-Inhibitor</td>
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<td>5</td>
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<tr>
<td>AII-Receptor Blocker</td>
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<td>3</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
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<td>2</td>
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Abbreviations: UC = usual care group, BF = treatment group
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<tr>
<th>ID</th>
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<td>ACE-I, BB</td>
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<td>ACE-I, BB</td>
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<td>B</td>
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<td>W</td>
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<td>W</td>
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<td>M</td>
<td>B</td>
<td>BB, CCB</td>
</tr>
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<td>W</td>
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<td>UC</td>
<td>69</td>
<td>M</td>
<td>W</td>
<td>N/A</td>
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</table>

Abbreviations: UC = usual care group, BF = treatment group, M = male, F = female, B = black, W = white, ACE-I = ACE-inhibitor, BB = beta blocker, ARB = AII-receptor blocker, CCB = Calcium Channel Blocker
Table III. Stress Assessment #1

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<tr>
<th></th>
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<th>S1</th>
<th>R1</th>
<th>S2</th>
<th>R2</th>
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<td><strong>USUAL CARE (UC) GROUP</strong></td>
<td></td>
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<tr>
<td>Respiration (breaths/min)</td>
<td>15.4 ± 0.6</td>
<td>13.8 ± 0.4</td>
<td>15.2 ± 0.8</td>
<td>13.0 ± 0.5</td>
<td>15.4 ± 0.4†</td>
</tr>
<tr>
<td>Temperature (°F)</td>
<td>82.4 ± 2.6</td>
<td>82.2 ± 2.6</td>
<td>82.4 ± 2.6</td>
<td>84.1 ± 2.5</td>
<td>81.0 ± 2.5</td>
</tr>
<tr>
<td>Skin Conductance (µS)</td>
<td>1.3 ± 0.3</td>
<td>2.1 ± 0.5</td>
<td>1.9 ± 0.4</td>
<td>2.5 ± 0.5</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>63.0 ± 3.2</td>
<td>68.7 ± 3.4</td>
<td>63.3 ± 3.1</td>
<td>68.1 ± 3.1</td>
<td>63.2 ± 3.0</td>
</tr>
<tr>
<td>SDNN (msec)</td>
<td>39.0 ± 4.2</td>
<td>32.6 ± 3.1</td>
<td>50.2 ± 6.2</td>
<td>39.6 ± 5.5</td>
<td>48.0 ± 5.0</td>
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<td><strong>BIOFEEDBACK (BF) GROUP</strong></td>
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<tr>
<td>Respiration (breaths/min)</td>
<td>13.6 ± 0.6</td>
<td>13.2 ± 0.6</td>
<td>14.7 ± 0.4</td>
<td>13.1 ± 0.5</td>
<td>13.9 ± 0.5</td>
</tr>
<tr>
<td>Temperature (°F)</td>
<td>89.3 ± 2.0*</td>
<td>89.7 ± 1.9*</td>
<td>90.2 ± 1.9*</td>
<td>90.5 ± 1.9*</td>
<td>90.1 ± 2.0*</td>
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<tr>
<td>Skin Conductance (µS)</td>
<td>1.7 ± 0.5</td>
<td>2.9 ± 0.8</td>
<td>2.3 ± 0.6</td>
<td>3.7 ± 0.9</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>59.4 ± 2.8</td>
<td>63.0 ± 2.9</td>
<td>59.8 ± 2.8</td>
<td>64.0 ± 3.2</td>
<td>59.9 ± 2.8</td>
</tr>
<tr>
<td>SDNN (msec)</td>
<td>39.4 ± 6.4</td>
<td>41.1 ± 8.0</td>
<td>46.4 ± 5.0</td>
<td>38.1 ± 6.0</td>
<td>51.3 ± 8.2</td>
</tr>
</tbody>
</table>

* p < 0.05 vs UC group. † p < 0.05 vs UC S2.
(SR) during the first stress assessment (SA1), the BF group had an average respiration rate of 13.6 ± 0.6 breaths per minute. The UC group had an average of 15.4 ± 0.6 breaths per minute, and the difference between the UC and BF group was not significant. During the first stressor (S1) of the first stress assessment, the BF group had an average respiration rate of 13.2 ± 0.6 breaths per minute. The BF group did not demonstrate the ability to recover nor lower their respiration rate during the first recovery period as their respiration rate increased to 14.7 ± 0.4 breaths per minute. During the first stressor, the UC group had an average respiration rate of 13.8 ± 0.4 breaths per minute, and like the BF group did not demonstrate the ability to recover as their respiration rate increased to 15.2 ± 0.8 during the first recovery period (R1). In regard to the second stressor (S2), the BF group had an average respiration rate of 13.1 ± 0.5 breaths per minute. Again, the BF group was unable to recover and lower their respiration rate as it increased to 13.9 ± 0.5 breaths per minute during the second recovery period (R2). The UC group, during the second stressor, had an average respiration rate of 13.0 ± 0.5 breaths per minute, and their respiration rate increased to 15.4 ± 0.4 breaths per minute during the second recovery. The increase in respiration rate during the second stressor was statistically significant for the UC group (p < 0.01) (Figure 9).

**Finger Temperature**

However, the Finger temperature recording, during the initial self relaxation period, yielded a temper of 89.3 ± 2.0 °F for the BF group and 82.4 ± 2.6 °F for the UC group. The difference between the two was statistically significant (p < 0.05) as shown in Figure 10. During the first stressor, the BF group had an average finger temperature of
Figure 9. UC Respiration Rate

The average respiration rate for the UC group during the second stressor of stress assessment one vs the average respiration rate for the UC group during the second recovery of the first stress assessment. n = 9 UC. ** p < 0.01.
Figure 10. Finger Temperature UC vs BF

Average finger temperature during self-relaxation of the first stress assessment in the UC group and BF group. n = 9 UC, 10 BF. * p < 0.05
89.7 ± 1.9 °F. Their finger temperature rose to 90.2 ± 1.9 °F during the first recovery period; however the change was not statistically significant. In regards to the UC group, during the first stressor their average finger temperature was 82.2 ± 2.6 °F and their finger temperature changed to 82.4 ± 2.6 °F. This change was not statistically significant. However, for both the first stressor (p < 0.05) and the first recovery period (p < 0.05), the BF group had statistically significantly higher average finger temperatures than the UC group, as shown in Figure 11 and Figure 12. During the second stressor, of the first stress assessment, the BF group had an average finger temperature of 90.5 ± 1.9 °F and during the second recovery period the BF group had an average finger temperature of 90.1 ± 2.0 °F. The difference was not statistically significant. In regard to the UC group, during the second stressor they had an average finger temperature of 84.1 ± 2.5 °F and during the second recovery period they had an average finger temperature of 81.0 ± 2.5 °F. The difference was not statistically significant. However, just as was the case in with the first stressor and recovery, during the second stressor (p < 0.05) and second recovery (p < 0.05) the BF group had statistically significantly higher average finger temperatures, as shown in Figure 13 and Figure 14.

**Skin Conductance**

In regard to skin conductance, during the self relaxation period of the first stress assessment the BF group had an average skin conductance of 1.7 ± 0.5 uS while the UC group had an average skin conductance of 1.3 ± 0.3 uS. During the first stressor, the BF group had an average skin conductance of 2.9 ± 0.8 uS and lowered their average to 2.3 ± 0.6 during the first recovery period. However, the change was not significant. In regard to
Figure 11. Finger Temperature UC vs BF S1

Average finger temperature of the UC and BF groups during the first stressor in the first stress assessment. n = 9 UC, 10 BF. * p < 0.05.
Figure 12. Finger Temperature UC vs BF R1

Average finger temperature of the BF and UC groups during the first recovery period of the first stress assessment. n = 9 UC, 10 BF. * p < 0.05.
Figure 13. Finger Temperature UC vs BF S2

Average finger temperature of the UC and BF groups during the second stressor of stress assessment one. n = 9 UC, 10 BF. * p < 0.05.
Figure 14. Finger Temperature UC vs BF R2

Average finger temperature of the UC and BF groups during the second recovery period of the first stress assessment. n = 9 UC, 10 BF. * p < 0.05.
the UC group, they had an average skin conductance of 2.1 ± 0.5 uS during the first stressor and reduced their average to 1.9 ± 0.4 uS during the first recovery period; the change was not significant. During the second stressor, the BF group had an average skin conductance of 3.7 ± 0.9 uS and lowered their average to 2.8 ± 0.7 uS during their recovery; the change was not statistically significant. The UC group had an average skin conductance of 2.5 ± 0.5 uS during the second stressor and lowered their average to 2.2 ± 0.4 uS during their recovery; however the change was not significant.

Heart Rate / Heart Rate Variability (SDNN)

In regard to heart rate, during the first self relaxation period the BF group had an average heart rate of 59.4 ± 2.8 beats per minute and the UC group had an average heart rate of 63.0 ± 3.2 beats per minute. The difference between the two was not statistically significant. During the first stressor the BF group had an average heart rate of 63.0 ± 2.9 beats per minute and lowered their average to 59.8 ± 2.8 beats per minute, however, the change was not statistically significant. During the first stressor the UC group had an average heart rate of 68.7 ± 3.4 beats per minute and lowered their average to 63.3 ± 3.1 beats per minute during the first recovery period. The change was not significant. During the second stressor, the BF group had an average heart rate of 64.0 ± 3.2 beats per minute and during the second recovery period they lowered their average to 59.9 ± 2.8 beats per minute. However, the change was not significant. The UC group, during the second stressor, had an average heart rate of 68.1 ± 3.1 beats per minute and lowered their heart rate to 63.2 ± 3.0 beats per minute, but the change was not statistically significant.
In regard to SDNN, during the first self relaxation period of the first stress assessment, the BF group had an average SDNN of 39.4 ± 6.4 and the UC group had an average SDNN of 39.0 ± 4.2. The difference between the two means was not statistically significant. During the first stressor, the BF group had an average SDNN of 41.1 ± 8.0 and increased their SDNN to 46.4 ± 5.0 during the first recovery period, but the change was not statistically significant. In regards to the UC group, their average SDNN during the first stressor was 32.6 ± 3.1 and their average SDNN during the first recovery period was 50.2 ± 6.2. The change was statistically significant (Figure 15). During the second stressor, the BF group had an average SDNN of 38.1 ± 6.0 and increased their average SDNN to 51.3 ± 8.2 during the second recovery period. The increase was not statistically significant. In regards to the UC group, their average SDNN during the second stressor was 39.6 ± 5.5 and increased to 48.0 ± 5.0 during the second recovery period; the change was not significant.

3.3 Stress Assessment 2: Physiological Data

Respiration Rate

The interaction between time and treatment (F (5, 80) = 3.937, p = .003) was significant on respiration rate. From post-hoc testing and visual inspection of Figure 16, participants who received BFSM had significantly lower respiration rates over time compared to participants in the UC group. The difference was most notable in the self relaxation and recovery periods of stress assessment two compared to stress assessment one. This reveals that participants in the BFSM group successfully learned to reduce their
Figure 15. SDNN UC Stressor 1 vs Recovery 1

The average SDNN in the UC group during the first stressor vs the first recovery period. 
n = 9 UC.  * p < 0.05.
Figure 16: Respiration Rate Across all Timepoints

Timepoint 1 is the average respiration rate during the self relaxation from stress assessment one. Timepoint 2 is the average respiration rate of the two stressors during stress assessment one, and timepoint 3 is the average respiration rate of the two recovery periods of stress assessment one. Timepoint 4 is the average respiration rate during the self relaxation from stress assessment two. Timepoint 5 is the average respiration rate of the two stressors during stress assessment two, and timepoint 6 is the average respiration rate during the recovery periods of stress assessment two.
respiration rate, while the participants in the UC group did not. Additionally, the main effect of time (F (5, 80) = 4.324, p = .002) and the main effect of treatment (F (1, 16) = 16.907, p = .001) were significant. This indicates that the time had an effect on respiration rate and that the BFSM had different respiration rates than the UC group.

**Finger Temperature**

The sphericity assumptions were not met for this analysis (Mauchly's W = 0.00, x² = 138.76, p = .000). Because of this, a Greenhouse-Geisser transformation of the df was used. Neither the interaction between time and treatment (F (1.261, 21.433) = .258, p = .671) nor the main effect of time (F (1.261, 21.433) = .472, p = .543) was significant. However, the between-subject main effect of treatment was significant (F (1, 17) = 12.708, p = .002). As displayed in Figure 17, participants in the UC had significantly higher finger temperatures compared to the participants in the BFSM group according to post-hoc pairwise t-testing.

**Skin Conductance**

The sphericity assumptions were not met for this analysis (Mauchly's W = 0.00, x² = 127.01, p = .000). Because of this, a Greenhouse-Geisser transformation of the df was used. Neither the interaction between time and treatment (F (1.275, 21.678) = .606, p = .483) nor the between-subject effect of treatment (F (1, 17) = 1.113, p = .306) was significant. However, the within-subjects effect of time was significant (F (1.275, 21.678) = 11.102, p = .002). As displayed in Figure 18, participants in both the UC and BF group
Figure 17: Finger Temperature Across all Timepoints

Timepoint 1 is the average finger temperature during the self relaxation from stress assessment one. Timepoint 2 is the average finger temperature of the two stressors during stress assessment one, and timepoint 3 is the average finger temperature of the two recovery periods of stress assessment one. Timepoint 4 is the average finger temperature during the self relaxation from stress assessment two. Timepoint 5 is the average finger temperature of the two stressors during stress assessment two, and timepoint 6 is the average finger temperature during the recovery periods of stress assessment two.
Figure 18: Skin Conductance Across all Timepoints

Timepoint 1 is the average skin conductance during the self relaxation from stress assessment one. Timepoint 2 is the average skin conductance of the two stressors during stress assessment one, and timepoint 3 is the average skin conductance of the two recovery periods of stress assessment one. Timepoint 4 is the average skin conductance during the self relaxation from stress assessment two. Timepoint 5 is the average skin conductance of the two stressors during stress assessment two, and timepoint 6 is the average skin conductance during the recovery periods of stress assessment two.
had significantly higher Skin Conductance during the stressor when compared to either the self-relax or recovery period according to post-hoc pairwise t-testing.

**Heart Rate**

The sphericity assumption was not met for this analysis (Mauchly's W = 0.00, \(\chi^2 = 188.85, p = .000\)). Because of this, a Greenhouse-Geisser transformation of the df was used. Neither the interaction between time and treatment (F (1.353, 21.640) = 1.185, p = .306), nor the main effect of treatment (F (1, 16) = 1.365, p = .260) was significant. However, the within-subject effect of time (F (1.353, 21.640) = 6.984, p = .009) was significant. As displayed in Figure 19, participants in both the UC and BF group had significantly higher heart rates during the stressor when compared to either the self-relax or recovery period according to post-hoc pairwise t-testing.

**SDNN**

Neither the interaction between time and treatment (F (5, 80) = .168, p = .974) nor the between-subject effect of treatment (F (1, 16) = 0.028, p = .868) was significant. However, the within-subject effect of time was significant (F (5, 80) = 3.066, p = .014). As displayed in Figure 20, participants in both the UC and BFSM group had significantly lower SDNN during the stressor when compared to either the self-relax or recovery period according to post-hoc pairwise t-testing.
Figure 19: Heart Rate Across all Timepoints

Timepoint 1 is the average heart rate during the self relaxation from stress assessment one. Timepoint 2 is the average heart rate of the two stressors during stress assessment one, and timepoint 3 is the average heart rate of the two recovery periods of stress assessment one. Timepoint 4 is the average heart rate during the self relaxation from stress assessment two. Timepoint 5 is the average heart rate of the two stressors during stress assessment two, and timepoint 6 is the average heart rate during the recovery periods of stress assessment two.
Figure 20: SDNN Across all Timepoints

Timepoint 1 is the average SDNN during the self relaxation from stress assessment one. Timepoint 2 is the average SDNN of the two stressors during stress assessment one, and timepoint 3 is the SDNN of the two recovery periods of stress assessment one. Timepoint 4 is the average SDNN during the self relaxation from stress assessment two. Timepoint 5 is the average SDNN of the two stressors during stress assessment two, and timepoint 6 is the average SDNN during the recovery periods of stress assessment two.
3.4 Blood and Questionnaire Data

Blood Data

A series of six mixed model two (treatment: BFSM, UC) by two (time: SA1, SA2) repeated measures ANOVAs were conducted to evaluate the effects of treatment over time on biological markers of sympathetic activity and inflammation. The dependent variables included norepinephrine, epinephrine, dopamine, CRP, MPO and TNF-a. As previously mentioned, for all variables normality assumptions were met. Because there were only two time points the sphericity assumption could not be evaluated. See Table IV for a summary of descriptive statistics for both groups across stress assessment one and stress assessment two. As shown in Table IV, there were no significant within subject time by treatment interaction effects. There were also no significant main effects of time or treatment. However, several variables approached significance or clinical relevancy. These included norepinephrine and TNF-a. Figure 21 shows that norepinephrine was approaching a significant main effect for treatment, and Figure 22 shows that TNF-a was approaching a significant main effect for time.

Questionnaire Data

A series of five mixed model two (treatment: BFSM, UC) by two (time: SA1, SA2) repeated measures ANOVAs were conducted to evaluate the effects of treatment over time on questionnaires measuring for psychological distress. The dependent variables included scores from the SF-36 physical, SF-36 mental, LET, GAD-7 and PHQ-8. For all variables, all normality assumptions were met, and because there were only two time points the sphericity assumption could not be evaluated. See Table IV for a summary of
**Table IV: ANOVA F and P Values for Blood and Questionnaire Data**

<table>
<thead>
<tr>
<th>Blood Values</th>
<th>Within-subject effects</th>
<th>Between-subject effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time*Treatment</td>
<td>Time</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.286</td>
<td>0.601</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.147</td>
<td>0.707</td>
</tr>
<tr>
<td>Dopamine</td>
<td>0.232</td>
<td>0.637</td>
</tr>
<tr>
<td>CRP</td>
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<td>0.39</td>
</tr>
<tr>
<td>MPO</td>
<td>0.07</td>
<td>0.796</td>
</tr>
<tr>
<td>TNF-a</td>
<td>0.08</td>
<td>0.782</td>
</tr>
<tr>
<td>Questionnaires</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 Physical</td>
<td>0.09</td>
<td>0.769</td>
</tr>
<tr>
<td>SF-36 Mental</td>
<td>2.271</td>
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</tr>
<tr>
<td>LET</td>
<td>2.928</td>
<td>0.105</td>
</tr>
<tr>
<td>GAD-7</td>
<td>0.003</td>
<td>0.957</td>
</tr>
<tr>
<td>PHQ-8</td>
<td>0.671</td>
<td>0.424</td>
</tr>
</tbody>
</table>
Figure 21: Norepinephrine SA1 vs SA2

Shows norepinephrine levels from stress assessment one to stress assessment two in the BFSM and UC groups.
Figure 22: TNF-a SA1 vs SA2

Shows TNF-a levels from stress assessment one to stress assessment two in the BFSM and UC groups.
descriptive statistics for both groups across stress assessment one and stress assessment two. As shown in Table IV, there were no significant within subjects time by treatment interaction effects. However, the SF-36 mental had a significant main effect of time (p = 0.047) and a significant main effect of treatment (p = 0.048), and the GAD-7 had a significant main effect of time (p = 0.001). As shown in Figure 23, both the UC and BFSM groups increased scores from stress assessment one to stress assessment two and the BFSM group increased their scores more than the UC group. However, the interaction was not significant. Figure 24 shows that both the BFSM and UC groups had significantly lower scores at stress assessment two compared to stress assessment one.
Figure 23: SF-36 Mental Aggregate Scores SA1 vs SA2

Scores from stress assessment one to stress assessment two in the BFSM and UC groups.
Figure 24: GAD-7 Scores SA1 vs SA2

Scores from stress assessment one to stress assessment two in the BFSM and UC groups.
CHAPTER IV
DISCUSSION

Inflammation, psychological distress and poor heart function are known to accompany CAD. While there are numerous drugs which help reduce these symptoms, sometimes the drugs themselves have undesired side effects. Therefore, complementary forms of treatment, such as stress management and biofeedback, have begun to be explored as possible treatments which can be effective in reducing the symptoms of CAD, without the negative side effects. This study examined whether BFSM could have a positive effect on inflammation, psychological distress, and/or poor heart function.

4.1 BFSM and the Autonomic Nervous System

*Stress Assessment One: Self Relaxation*

When the patients arrived for the first stress assessment, they completed a mental stress test. The first five minutes of the stress test was devoted to recording the patients, at their baseline level, and asking them to simply relax to the best of their ability. The goal was to see how well the patients could relax on their own, when they started the
study. During the five minutes, we recorded their respiration rate, finger temperature, skin conductance, heart rate, and SDNN, which are all indicators of stress.

During this initial five minute period we found that the patients who were in the BF group had an average respiration rate of 13.6 ± 0.6 breaths per minute, while the patients in the UC group had an average respiration rate of 15.4 ± 0.6 breaths per minute. The BF group had a significantly lower respiration rate than the UC group (p < 0.05) but both groups were still well above the desired respiration rate of 6 ± 1 breaths per minute; meaning the BF patients had a lot of room for improvement over the course of the training sessions.

In regard to finger temperature, during the baseline five minute period the BF group had a significantly higher (p < 0.05) average temperature, with an average of 89.3 ± 2.0 °F, compared to the UC group which had an average temperature of 82.4 ± 2.6 °F. The large difference between the BF group and the UC group meant that at baseline the BF group had a finger temperature close to what they would be taught to reach during BFSM. Therefore, the BF group did not have as much room for improvement as the UC group.

The five minute baseline period revealed that the BF group started with an average skin conductance level of 1.7 ± 0.5 uS and the UC group had a skin conductance of 1.3 ± 0.3 uS. These averages were not significantly different from each other but they indicated that both groups started with a skin conductance level in a range below 3.0 uS, which is considered to be a level indicating a relaxed state. Therefore, in regards to skin conductance the patients did not have much, if any, room for improvement.
explanation for the lack of reactivity could be the abundance of drug the CAD patients were taking.

When examining heart rate during the self relaxation, the BF group had an average of 59.4 ± 2.8 beats per minute, while the UC group had an average heart rate of 63.0 ± 3.2 breaths per minute. The difference was not statistically significant and both groups had a relatively low heart rate, indicating that at baseline the patients were able to relax their hearts to a desired rate. This meant that there was not a lot of room for improvement during BFSM. However, a possible explanation may be that the patients were taking a number of drugs which may influence their heart rate.

Finally, during the self relaxation baseline period the BF group had an average SDNN of 39.4 ± 6.4 and the UC group had an average SDNN of 39.0 ± 4.2; the differences were not significant. These results were slightly higher than those found in prior study, which found CAD patients had baseline SDNN levels of 28.0 ± 15.5 in the treatment group and 33.0 ± 12.6 in their usual care group (Del Pozo, Gevirtz, Scher, 2004). However, Del Pozo was able to raise the SDNN of the patients in his treatment group, after 18 weeks of breathing training and heart and respiratory physiologic biofeedback, to an average of 42.0 ± 25.8. This leads one to conclude that even though the BF patients in our study started with a higher SDNN than the patients in the Del Pozo study, there might still be room for improvement.

**Stress Assessment One: Stress Response**

After the five minute baseline, the patients went through a series of two mental stressors, lasting 90 seconds each, and each was directly followed by a 5 minute recovery
period during which the patients were asked to attempt to relax themselves as best they could following the stressor.

During this period, in regards to respiration rate, neither the BF nor the UC group demonstrated a lot of reactivity. During the first stressor, the BF group had an average respiration rate of 13.2 ± 0.6 breaths per minute and during the first recovery period they had an average respiration rate of 14.7 ± 0.4 breaths per minute. During the first stressor, the UC group had an average respiration rate of 13.8 ± 0.4 breaths per minute and during the first recovery they had an average respiration rate of 15.5 ± 0.8 breaths per minute. During the second stressor, the BF patients had an average respiration rate of 13.1 ± 0.5 breaths per minute and an average respiration rate of 13.9 ± 0.5 breaths per minute during the second recovery. During the second stressor the UC patients had an average respiration rate of 13.0 ± 0.5 and during the second recovery had an average of 15.4 ± 0.4 breaths per minute; this was the only significant change. However, the respiration rate increased during the recovery, indicating that the UC patient’s respiration rates changed in the undesired direction. These results suggest that the stressors did not have an affect on respiration rate in either group, and during the recovery neither group was able to slow their breathing. While it would have been expected for the stressor to increase the respiration rate, the fact that the patients were unable to slow their breathing during the recovery indicated that there was plenty of room for improvement during BFSM. One possible explanation for the lack of response, during the stressors, was that the patients were required to talk during each stressor. Therefore, their respiration rate may have been affected by how fast, or how slowly, they were talking.
When examining finger temperature during the stressors and recovery periods, the BF and UC groups demonstrated little change throughout the assessment. However, the BF group had a consistently higher finger temperature than the UC group throughout the assessment. The BF group had an average finger temperature of 89.7 ± 1.9 °F during the first stressor and 90.2 ± 1.9 °F during the first recovery. This was followed by an average finger temperature of 90.5 ± 1.9 °F during the second stressor and 90.1 ± 2.0 °F during the second recovery. Neither of these changes were significant. The UC group had temperatures of 82.2 ± 2.6 °F during the first stressor and 82.4 ± 2.6 °F during the first recovery, followed by temperatures of 81.4 ± 2.5 °F and 81.0 ± 2.5 °F during the second stressor and second recovery, respectively. It is clear that for both groups, neither stressor was able to cause enough stress to significantly reduce finger temperature, nor were the patients able to raise their finger temperature during the recovery periods. It is noteworthy that the patients in the BF group had significantly higher average temperatures during each period of the stress assessment. The BF patients, throughout the stress assessment had finger temperatures close to, or above, 90 °F which is the temperature they would be taught to strive for during BFSM. Therefore, the BF patients had little room for improvement while the UC patients had plenty. A possible explanation for the lack of reactivity could be that finger temperature is typically slower to react than the other physiologic parameters. This means that our 90 second stressors may not have been long enough to allow for a response.

For skin conductance, the patients in both groups demonstrated very little reactivity throughout the stressor and recovery periods. The BF group had an average skin conductance of 2.8 ± 0.8 uS during the first stressor and 2.3 ± 0.6 uS during the first
recovery, and followed up with skin conductance levels of 3.7 ± 1.6 uS and 2.8 ± 1.1uS during the second stressor and second recovery, respectively. This indicated that the BF group had some minor responses to the stressors and were able to make minor improvements during the recovery periods, but nothing significant. As noted earlier, with prior physiological data, the stressors seemed unable to stress the BF patients to a point that creates a large physiological response. The UC patients responded in a similar pattern to the BF patients, as their average skin conductance remained low throughout the stressors and recovery periods. Further, they demonstrated minor, if any, responses to the stressors and minor ability to recover from the little stress that they demonstrated. Therefore, in regards to skin conductance during the first stress assessment, the patients in both groups appeared to remain calm throughout the assessment but demonstrated minor reactions to the stressors, which they were able to bring back down close to baseline levels during the recovery periods.

When examining heart rate during the stressor and recovery periods, the patients in the BF group had average heart rates of 63.0 ± 2.9 and 59.8 ± 2.9 during the first stressor and first recovery. They followed those numbers with average heart rates of 64.0 ± 3.2 and 59.9 ± 2.8 during the second stressor and second recovery. Similar to their results with skin conductance, the BF group had average heart rates which indicated they did not become overly stressed during the assessment. However, they did show a minor reaction during the stressors and the ability to recover during the recovery periods. Further, because they had such low heart rates throughout the assessment, there was little room for improvement during BFSM. In regards to the UC patients, they had similar results to the BF group in that overall they had heart rates which indicated they remained
calm throughout the assessment. They also demonstrated minor responses to the stressors (68.7 ± 3.4 for stressor one and 68.1 ± 3.1 for stressor two) but were able to recover from the little response they experienced (63.3 ± 3.1 in recovery one and 63.2 ± 3.0 during recovery two).

The last physiological measure examined was SDNN. The SDNN for both groups acted in a similar pattern to the heart rate. The BF patients had an average SDNN of 41.1 ± 8.0 and 46.4 ± 5.0 during the first stressor and first recovery. During the second stressor and second recovery the BF patients had an average SDNN of 38.1 ± 6.0 and 51.3 ± 8.5 respectively. While there did appear to be a minor reaction to the stressors, nothing was significant. However, the BF patients were able to recover from the minor stress they did feel during the recovery periods. Therefore, because the BF patients demonstrated such a minor response to the stressors and an ability to recover from those stressors, they did not have a lot of room for improvement. The UC patients, interestingly, demonstrated a response in the first stressor and the ability to recover during the first recovery period. They had an average SDNN of 32.6 ± 3.6 and 50.0 ± 6.2 during the first stressor and first recovery, and the change was statistically significant (p < 0.05). However, during the second stressor and recovery, the UC patients had averages of 39.6 ± 5.5 and 48.0 ± 5.0, which did not yield a significant change.

*Stress Assessment Two*

When examining respiration rate, there was a significant interaction (p = 0.003), and a significant main effect for time (p = .002) and main effect for treatment (p = .001). This indicates that BFSM did teach the patients to breath at lower levels than patients in
the UC group. This data also shows that time had an effect on respiration rate, but more importantly that the BF group had significantly lower respiration rates than the UC group over time, due to the treatment, and that the BF patients could execute that skill without the aid of a biofeedback coach. This is encouraging because learning how to control one’s respiration is a vital skill involved in BFSM and if one can learn to regulate their respiration rate, it can have positive effects on the other physiological markers of stress reactivity.

When examining the finger temperature response, there was a statistically significant main effect of treatment. This indicates that the patients in the BF group had different finger temperatures than the UC patients. However, the BF patients came into the study with significantly higher finger temperatures than the UC group. This indicates that there was not an effect of treatment over time, simply that the BF patients had a higher finger temperature when they started and when they finished the study compared to the UC group. A possible explanation for their performance was that the BF group started at such a high finger temperature throughout the first stress assessment, that there simply was not much room for them to improve. On average, throughout the first stress assessment the BF patients collectively had finger temperatures close to 90 °F which is a temperature they were taught to maintain during BFSM. Therefore, while they did not improve, they did demonstrate the ability to maintain a high level of performance in the second stress assessment.

In regard to skin conductance, there was a significant main effect of time. This indicates that the BF and UC groups had a reaction to the stressors and were able to recover from them, but there was not a difference between the two groups. A possible
explanation was that both groups started with a low skin conductance during the first stress assessment, which did not leave the BF group room for improvement. It appeared as though the stressors did excite some enough reactivity, but not enough to demonstrate a clinically significant response, making it difficult to show improvement when there was minimal room to improve.

When examining heart rate reactivity, one can see a similar trend to the skin conductance results, as there was a significant main effect of time. This shows that the both groups had a reaction to the stressors and that they were able to recover, but BFSM did not have an effect on the change. However, throughout both stress assessments both the BF and UC group had heart rates in a desirable, healthy range. Therefore, once again there was not room for improvement. It is possible that given the disease of this study sample, through their own time involved in regular cardiac rehabilitation, they have become in touch with how their react in stressful situations and know that it is important to suppress high reactivity. However, another possible reason is that similar to the other parameters, the stressors were not strong enough to create a physiological reaction.

Finally, the BF and UC groups again did not have any significant differences between stress assessment one and stress assessment two, in regard to SDNN. There was a significant main effect of time, but that only indicated that both groups had a reaction to the stressors and recovered from them, but there was no difference between the two groups. This was particularly surprising because a prior study demonstrated that CAD patients could show improvement in SDNN after weekly biofeedback training (Del Pozo, Gevirtz, Scher, 2004). However, the patients in both the BF and UC groups in this study started at a higher average SDNN than the patients in the prior study. It is possible that
there is a ceiling effect for CAD patients in regards to their SDNN, and the patients in this study at an average close to that ceiling.

When examining the results from the physiological data as a whole, one might ask if BFSM was indeed successful. Through BFSM we were trying to lower their overall arousal, which was reflected in the baseline measurement during the stress assessments. It appeared as though BFSM was successful in improving overall arousal in regards to respiration, but there was not a significant change in the other parameters. We were also trying to teach the patients to respond less to stress, which was reflected in the stressor responses. The BF group did not show a difference in this category. However, in regard to respiration rate, part of the reason for that may have been the patients were required to talk during both stressors. Finally, we were trying to teach them to recover faster and more completely, which was reflected during the recovery periods following the stressors. Unfortunately, the BF did not show an ability to recover more efficiently than the UC group. However, in many cases the stressors were unable to entice a large physiological response, which most likely influenced the recovery data. It appears as though the structure of our stress assessment, in most cases failed to bring about enough stress to create a physiological response. However, one possible explanation could be that given the stress patients in cardiac rehab have dealt with, asking them to perform sort mental stress tasks in a research setting is too far beneath the stress they have become accustomed to that it is not possible to create a response. This indicates that it is possible that prior to enrolling subjects into a stress management study, patients should first be screened for levels of stress. This would eliminate the possibility of having patients enter a study with low markers of stress and stress reactivity.
4.2 BFSM and Blood Markers

As previously stated, when one is stressed they have increased sympathetic activity. Similarly, those with CAD have been shown to have an over activated sympathetic nervous system. Therefore, it is desired that CAD patients even out their autonomic nervous system and increase their parasympathetic activity while reducing sympathetic activity. In this study we attempted to achieve this goal through BFSM. Further, it has been shown that CAD patients have higher levels of inflammation which cause harm to the body. Tracy et al. (2002) demonstrated a connection between the sympathetic nervous system and inflammation, showing that the sympathetic nervous system plays a role in regulating inflammation in real time. Therefore, if BFSM can effectively reduce sympathetic activity, one can conclude that it would also reduce levels of inflammation. Markers of sympathetic activity and inflammation can both be found in the blood, and a blood draw was administered during the first and last session of all the patients in this study to test for markers of sympathetic activity and inflammation.

Markers of Sympathetic Activity

The markers for sympathetic activity which we tested were NE, EPI and dopamine. It was hypothesized that after BFSM training the BF patients would learn to regulate their autonomic nervous system and in turn have lower levels of sympathetic activity in the second stress assessment. We expected the UC group to have minimal change in the second stress assessment.
When comparing the levels we found in the first stress assessment to those found in other studies involving CAD patients, both the BF and UC groups had a higher average NE level (BF: 399 pg/ml UC: 543 pg/ml) compared to other studies (294 ± 188 pg/ml) (Makoto, Masahiko, Takamitsu et al. 2007). This might explain why the NE level was lower in the second stress assessment for both groups, as the patients may have simply reduced toward the mean. However, when examining the levels of EPI found in our study compared to other studies, the BF (EPI: 61 pg/ml) and UC (EPI: 72 pg/ml) patients again started at higher the levels found in other studies (43 ± 26 pg/ml) (Makoto, Masahiko, Takamitsu et al. 2007); but unlike NE, EPI either stayed the same (UC) or increased (BF). In regard to dopamine, their starting levels (BF: 20 pg/ml UC: 23 pg/ml) were similar to those found in other studies (22 ± 9 pg/ml) (Makoto, Masahiko, Takamitsu et al. 2007), and stayed consistent as they showed little change in stress assessment two. In conclusion, it appears the BFSM did not have an impact on markers of sympathetic activity, and the changes which did occur from stress assessment one to stress assessment two may have been due to normal fluctuations in sympathetic activity for CAD patients.

**Markers of Inflammation**

The markers of inflammation we tested were CRP, MPO and TNF-alpha. We expected that each of these markers would be reduced in stress assessment two compared to stress assessment one in the BF group, and that there would be minimal change in the UC group.

When comparing our results to those found in other studies testing for inflammation, in regard to CRP, the BF group (2.5 ± 0.8 mg/l) and UC group (3.1 ± 0.9
mg/l), each had similar averages to the average found in a different study (2.6 mg/l) (Roman, 2010). In regard to TNF-alpha, the BF group (2.4 ± 1.0 pg/ml) and UC group (2.1 ± 1.1 pg/ml) had similar levels to those found in a different study by Safranow et al. as they had an average TNF-alpha level of 1.9 ± 1.1 pg/ml (Safranow, Dziedziejko, Rzeuski, et al. 2009). However, the levels we obtained for MPO (BF: 273 pmol/l UC: 280 pmol/l) were not consistent with those found in a study by Roman et al. who found an average MPO level of 93 pmol/l. The UC and BF patients both had slightly lowered MPO results for the second blood draw, but they were still above the average found by Roman et al. In conclusion, BFSM did not show any effect on markers of inflammation and our blood results were consistent with other findings for CRP and TNF-alpha, but were raised in MPO, when compared to results from prior studies.

4.3 Tests for Psychological Distress

Patients with CAD have been found to have higher levels of psychological distress than the general population (Rozanski, Blumanthal, Davidson, et al. 2005). CAD patients have shown a lower quality of life, higher anxiety, and greater depression than people without CAD. In order to test if BFSM had an impact on any of these aspects of psychological distress the SF-36, PHQ-8, GAD-7 and LET were administered to patients in the BF and UC groups on their first and last session.

The SF-36 is broken into a physical and mental aggregate, each of which generates its own score. The national average score for both the physical and mental aggregate is 50 with a standard deviation of 10. When the patients were tested during their first stress assessment, the BF group had an average physical aggregate of 46.2 and
an average mental aggregate of 47.3, while the UC group had a physical aggregate of 47.5 and a mental aggregate of 55.5. Therefore, physically the patients in both the BF and UC groups were below the national average, and mentally the BF was below but the UC was above the national average. The BF group did not have significantly different change at the conclusion of the study, compared to initial scores, indicating that BFSM did not have an influence on SF-36 scores. However, while there was essentially no change in the physical aggregate, the BF group was able to improve their average on the mental aggregate by an average of 5.3 points to a score average of 53. There was a main effect for time ($p = 0.047$) and a main effect for treatment ($p = 0.048$), however the interaction was not significant. This indicates that there was a larger increase in score by the BF group but that the UC group improved over time as well, and thus, there was not an interaction. In summary, the BF group was able to improve their SF-36 mental score but possibly due to the small sample size, or the improvements made in the UC group after 10 weeks of cardiac rehabilitation, there was not a significant interaction.

In regard to the PHQ-8, scores range from 0-24 with cutoff points of 5, 10, 15 and 20 representing mild, moderate, moderately severe and severe depressive symptoms. BFSM did not have an effect on PHQ-8 score, as the BF and UC groups demonstrated hardly any change. When the patients first came in, both groups had an average below the first cutoff score of 5 (BF: $3.3 \pm 1.0$ UC: $1.9 \pm 1.0$). This demonstrated that as a whole the patients in both groups were not particularly depressed, and when they returned for the second stress assessment they remained relatively happy.

In regard to the GAD-7, scores range from 0-21 with cutoff points of 5, 10, and 15 which represent mild, moderate and severe anxiety. When examining the change
between the BF and UC groups, the BFSM did not have a significant effect on the GAD-7 scores. However, there was a time main effect indicating that due to the 10 weeks between taking the questionnaire, the patients in both groups had different scores at stress assessment two. When the two groups came in for the first stress assessment, the BF (3.7 ± 1.1) and UC (3.2 ± 1.9) groups had an average below the first cutoff point and they remained below the cutoff point at the second stress assessment. This indicates that the patients were not particularly anxious when they started and remained not anxious when they completed the study.

For the LET, scores range from 6-30, there are not any set cutoff points but higher scores indicate more sense of purpose and engagement in life. BFSM did not have an impact on LET scores and the BF and UC groups had similar scores when they completed the questionnaire at the second stress assessment. However, the patients in both groups had high scores, close to 30 at both stress assessments, indicating that the patients felt they had a purpose in life and were engaged.

4.4 Summary

The goal of this study was to examine if BFSM could improve psychological distress, markers in inflammation and sympathetic activity in the blood, and teach CAD patients to better manage their stress. In terms of psychological distress, the patients entered our study with surprisingly upbeat attitudes toward their disease, and lives as a whole. Therefore, examining the effect of BFSM on psychological distress was made difficult when considering the sample we obtained. When examining the effect BFSM had on blood markers of sympathetic activity and inflammation, it appears that in this
study we were unable to bring about positive change. However, when comparing our results to similar studies, it reveals that our study sample had fluctuating blood markers that were sometime inconsistent with prior findings. Finally, when asking the question if BFSM indeed improved our patient’s ability to manage their stress, results are inconclusive because we were unable to create a stress response during the stress assessments. Further research is needed to explore what kinds of stressors can create a physiological response in CAD patients, and if a response is created, can BFSM help the patients to manage their stress in the future.

It is also important to note that data from the BFSM training sessions, for the BF patients, has yet to be analyzed. These data may show that some patients did better with training, and at that point we may want re-analyze the data, exploring the possibility of dividing the BF group into subgroups of those who were successful with training, and those who were not.
REFERENCES


