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Acute Effect of Intermittent Pneumatic Compression (ipc) on Inflammation, Circulation And Glucose Regualtion In

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Cleveland State University

ACUTE EFFECT OF INTERMITTENT PNEUMATIC COMPRESSION (IPC) ON INFLAMMATION, CIRCULATION AND GLUCOSE REGUALTION IN TYPE 2 DIABETICS

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ABSTRACT

Purpose: The purpose of this study is to determine whether Intermittent Pneumatic Compression (IPC) acutely improves inflammation and glucose regulation in Type 2 diabetics. It was hypothesized that acute use of pneumatic compression will improve circulation and glucose levels and decrease inflammation in Type 2 diabetics. **Methods:** Subjects included 10 individuals clinically diagnosed with Type 2 diabetes. Plasma and serum were obtained intravenously to analyze insulin, Interleukin-6 (IL-6), C-reactive protein (CRP) and nitric oxide (NO). An HbA1C was obtained at the beginning of testing via a finger stick. Subjects came into the laboratory a total of 2 times (on a Monday and Friday in the same week) to measure the variables previously listed and receive treatment. The subjects completed a total of 5 days (3 at home) of IPC treatments using the NormaTec recovery system. **Results:** There were no significant differences found within the inflammation values. Blood glucose levels decreased more in the laboratory setting than at home or on the subjects control days. Ten minute recovery blood glucose levels (-2.60 ± 3.01) decreased significantly ($p < 0.05$) in the laboratory setting. **Conclusion:** The hypothesis was supported because of the significant decrease of blood glucose in the recovery phase and the slight, nonsignificant decreases in Nitrate levels. There were also small, nonsignificant decreases in IL-6 and CRP levels observed over 5

days of treatment. Five days of treatment led to a decrease of basal levels of inflammation.

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CHAPTER I

INTRODUCTION

Background

Diabetes is an epidemic that affects more than 170 million individuals around the world (Stumvoll et al., 2005). There are two common types of diabetes, Type 1 and Type 2. Type 1 accounts for about 5% of all cases and is usually diagnosed at a young age. Individuals with Type 1 cannot produce insulin to maintain blood sugar levels. Type 2 usually develops later in life and can be a result of poor diet, inactivity or pre-existing conditions. These individuals are insulin resistant, which means the insulin that is being produced is not being recognized by the body. It is important for diabetics to monitor insulin levels. The pancreas produces insulin to lower glucose levels in the blood.

High blood glucose levels can cause inflammation of the blood vessels and other complications. Inflammation is a prominent risk factor for both cardiovascular disease and insulin resistance (Haffner 2006). Inflammatory biomarkers are useful for monitoring chronic disease activity and can predict mortality in individuals with Type 2 diabetes (Singh-Manoux et al., 2017). Interleukin-6 (IL-6) and C-Reactive Protein (CRP) are two common biomarkers that test for inflammation in the blood. When these markers are

high, there is a higher chance the individual has Type 2 diabetes mellitus (Shoelson el al., 2006).

Nitric oxide (NO) plays a key role in Type 2 diabetes. NO is a regulatory molecule with vascular, metabolic and cellular effects. Disturbances of NO generation may be a consequence of insulin resistance, which in turn, can also affect vascular response. Previous research has shown that nitric oxide can mediate IL-1β induced impairment and can lead to β-cell death (Kaneto et al., 1995).

Intermittent Pneumatic Compression (IPC) is a boot-like device that uses pulsation and inflating techniques around the limbs to improve venous circulations in individuals with varying types of diseases/issues such as diabetes, deep vein thrombosis, edema, etc. Traditionally, IPC was used to treat patients with coronary artery disease. Research shows that IPC significantly improved peripheral vascular function (Braith et al., 2010). Today, IPC is primarily used for treatment of deep vein thrombosis (DVT) and to improve circulation in patients with lower extremity arterial disease (Chen et al., 2001). Martin and Braith (2012) determined external counterpulsation (EECP) decreases circulatory markers of inflammation in subjects with abnormal glucose tolerance (AGT).

Diabetics have to self-monitor their blood glucose levels multiple times a day, usually requiring intermittent capillary blood sampling. Many barriers come along with doing so such as the pain of the finger prick and the frequency of testing. The Freestyle Libre system, a continuous glucose monitoring system, contains a sensor and a handheld device. The sensor is placed on the back of the arm and a thin, flexible filament goes under the skin. The handheld device is placed on top of the sensor and gives a glucose

reading in seconds. This CGM is the only 14-day device clinically proven to reduce time in hypoglycemia (Bolinder et al., 2016).

Purpose

The purpose of this study is to determine whether Intermittent Pneumatic Compression (IPC) acutely improves inflammation and glucose regulation in Type 2 diabetics.

Hypothesis

Acute use of pneumatic compression will increase nitric oxide levels and decrease blood glucose levels and inflammation in Type 2 diabetics.

CHAPTER II

LITERATURE REVIEW

Inflammatory Markers and Glucose Regulation

Affecting over 415 million people, Type 2 Diabetes (T2D) is a major global health issue (Nolan, 2011). Inflammation is a crucial factor in the development of Type 2 Diabetes. At the cellular level, metabolic changes alter functionality of tissues and cells which in turn alters inflammatory reactions. Inflammatory biomarkers include high sensitivity C reactive protein (hsCRP), interleukin-6 (IL-6) and cytokines (Herder, 2013). These biomarkers are useful for indicating infection and for monitoring chronic disease. CRP and IL-6 have been shown to predict mortality and cardiovascular outcomes (Kaptoge, 2010).

Glycemic control is an important factor that Type 2 Diabetics must worry about every day. About half of patients with T2D are unable to achieve adequate glycemic control (Suh, 2010). Increased endogenous glucose production (EGP) is a major source of hyperglycemia in Type 2 Diabetes. EGP is suppressed by both insulin and glucose in non-diabetics, but this effect in significantly impaired in individuals with type 2 diabetics (Campbell, 1988). Several studies have shown that the central nervous system (CNS) is involved in the regulation of glucose metabolism through its detection of nutrients and

hormones, signaling through hypothalamic ATP-sensitive potassium channels and transduction of those signals to the liver (Carey, 2013).

Singh-Manoux, et.al. (2013) examined whether AGP is a better biomarker of mortality risk than CRP and IL-6. The researchers recruited a total of 10,308 people (6895 mean and 3413 women), ages 35-55, during the years 1985-1988. Follow-ups took place every 5 years. The response rate was 73%. All subjects were employed by the British civil service in London. Between the years of 1997-1999, biomarkers were assayed from fasting serum samples. Covariates were drawn from the 1997-1999 assessment. Demographic covariates included age, sex and socioeconomical status. Health behavior covariates included smoking status, alcohol consumption, physical activity and dietary behavior. Chronic disease burden was assessed by prevalence of diabetes mellitus, cancer, cardiovascular disease, and chronic obstructive pulmonary disease. A total of 6551 subjects underwent clinical assessment in 1997-1999. 736 deaths occurred over a mean follow-up of 16.7 years. Results showed there was a correlation between AGP and IL-6 and a correlation between CRP and IL-6. AGP was associated with all-cause and cancer related mortality in the short-term but not in mortality beyond 5 years. When comparing all inflammatory markers, AGP wasn't even reliable in the short-term. Both CRP and IL-6 were associated with all-cause and cancer related mortality and CRP was associated with cardiovascular mortality. Overall, research showed that IL-6 may be the best indicator of of long-term health status and CRP and IL-6 are more important predictors of mortality.

Malencia, et. al. (2017) analyzed the long-term impact of altered metabolism on the level of mediators of inflammatory response in female patients with Type 2 Diabetes.

Females have a greater risk of mortality and hospitalizations even though more men have Type 2 Diabetes. A total of 204 subjects were involved in the study (97 patients with T2D and 107 non-diabetic patients). All subjects had arterial blood pressure, height, weight and waist circumference measured. Blood samples were drawn after an 8-hour fast. HbA1C, CRP and IL-6 were measured. Among the diabetic group, mean BMI and WHR were significantly higher than the non-diabetic control group. Subjects with T2D had significantly higher fasting plasma glucose and HbA1C than non-diabetic subjects. Median levels of CRP, IL-6 and cytokines were significantly higher in diabetic patients which supports the result of HbA1C being positively correlated with CRP. Also, BMI was positively and significantly correlated with IL-6. The researchers concluded that the concentration of many of the inflammatory markers at an acute phase correlates with the development of characteristics associated with T2D (obesity, insulin resistance, and diabetic complications).

Mihai, et. al. (2018) identified predictors of insulin resistance and correlation between insulin resistance and cardiovascular disease. In diabetic patients, heart attack risk is 2.13 fold higher for men and 2.95 fold higher for women than in population without diabetes. 121 newly diagnosed diabetic patients were included in this study. Subjects had to be over the age of 18, not receiving therapy and not be on any lipid lowering medications. Baseline testing was done to determine BMI, abdominal circumference, blood pressure, serum lipid concentrations and their resistance to insulin using the HOMA-IR (Homeostatic Model Assessment of Insulin Resistance). To be considered as significant for insulin resistance, the cut-off value for HOMA-IR was 2.5. Out of the 121 patients, 44 had a HOMA-IR of less than 2.5 and 77 had a HOMA-IR of

over 2.5. Patients under 2.5 were classified as non-insulin resistance and patients over 2.5 were classified as insulin resistant. Patients that were classified as insulin resistant had a mean systolic and diastolic BP significantly higher than patients that were non-insulin resistant. Patients that were insulin resistant also had significantly higher BMI, triglyceride and cholesterol levels and HbA1C. Researchers concluded that triglycerides and cholesterol (both HDL and non-HDL) can be used as indicators of insulin resistance.

Wang, et. al (2012) investigated the characteristics of glucose fluctuations in subjects with normal glucose tolerance, impaired glucose regulation and newly diagnosed, drug-naïve T2D. Fifty-three subjects with impaired glucose regulation (IGR), 56 subjects with newly diagnosed T2D and 53 subjects with normal glucose tolerance participated in this study. All participants performed a 75 g oral glucose tolerance test (OGTT). Fasting plasma glucose levels were measured at the half hour, hour, two hour and three hour mark. The CGMS System Gold was used in this study. This glucose sensor was inserted into the subcutaneous tissue of the abdomen to monitor glucose levels of interstitial fluid for 3 consecutive days. Subjects also did fingerstick to measure blood glucose levels. These measurements were used to test the CGMS accuracy. All subjects were to follow a strict meal method. The total caloric intake from the 3 daily meals was about 30 kcal/kg per day with about 50% carbohydrates, 15% proteins and 35% fat. Subjects were not allowed to eat between the 3 meals and had to refrain from alcohol, tea and coffee. There were no significant differences between the CGMS and finger stick values. Mean glucose levels before and after meals were higher in the drug-naïve group than any other group. This group also showed more excursions after breakfast, lunch and dinner. The drug-naïve group also had higher overnight glucose

concentrations and the other two groups remained consistent. Overall, glucose fluctuations gradually increase from normal glucose tolerance to impaired glucose regulation and impaired glucose regulation to newly diagnosed T2D. All newly diagnosed patients had higher glucose levels overnight and more intraday fluctuations.

Continuous Glucose Monitoring Systems

In 1994, CGMS was first studied in human subjects. In early studies, researchers studied the design of the sensor, techniques for inserting the sensor and the design of accessory components (Gross & Mastrototaro, 2000). In 1997, a study was conducted of the CGMS at four clinical sites across the United States. This study was designed to demonstrate the accuracy of the CGMS as a blood glucose tracking device, compare performance of patient inserted sensors vs. those inserted by the healthcare team and establish the duration of use for the sensor. Participants consisted of 62 subjects that had a history of diabetes. The subjects wore sensors for up to three weeks and were asked to also perform at least 11 blood glucose meter measurements each day. Measurements were taken before each meal, 1 and 2 hours after each meal and before bedtime. A total of 415 sensors were used during the study. Results showed that the average duration of sensor function was 69 hours. When comparing the CGMS and the meter measurements, the sensor showed close agreements to the blood glucose meter readings. Results also showed that sensor performance remained stable over the functional life of the device. There was no significant difference seen between participant sensor insertion and healthcare insertion. Gross and Mastrototaro concluded that CGMS is reliable and stable overtime and predictive of HbA1C. Although CGMS should be used in supplement with SMGB, CGMS has a potential to improve clinical outcomes in diabetes.

Tanenberg, et. al. (2004) studied the use of continuous glucose monitoring systems (CGMS) to guide therapy in patients with insulin treated diabetes. The purpose of this study was to show improved glycemic control with adjustments to the participants diabetes management plans based on either CGMS or self-monitoring of blood glucose (SMBG). This study consisted of 128 participants that had insulin treated diabetes and a HbA1C higher than 7.9%. Participants were assigned either to the CGMS or SMBG group. Both groups were instructed to perform capillary blood glucose measurements four times a day and in response to hypoglycemia for the entire study. The CGMS group additionally wore monitors for 3 days during weeks 1 and 3. Values were analyzed and used to adjust the subject's diabetes management plans. Results showed that the CGMS group showed improvements in both HbA1C and reduction in hypoglycemia compared to the SMBG group. The researchers concluded that CGMS guided therapy can be used to improve glycemic control in diabetics.

Intermittent Pneumatic Compression

Since the early 1800's, scientists have been looking at ways to improve circulation by using compression techniques. In 1934, Mont Reid and Louis Herrmann came up with the idea of using an alternating pressure and suction device which they called "PAVAEX". This device was said to treat various forms of lower extremity arterial diseases (Chen, 2001). Today, IPC devices are used to prevent deep vein thrombosis and treat ulcers, lymphoedema and venous insufficiency.

Salek, Bahrpeyma & Mohajeri-Tehrani (2015) evaluated the effects of IPC therapy on two aspects of balance dysfunction, one of the most important clinical signs of diabetic neuropathy. Thirty-nine neuropathic patients with type 2 diabetes for 5-15 years

and between the ages of 40 and 75 years participated in this study. This age range was used because the highest prevalence of T2D is in this age range. The participants were divided into two groups; intervention and control groups. A questionnaire on general information was given to all participants and they all went through other tests such as a vision test, HbA1c, fasting blood glucose, blood pressure and balance examinations (functional and dynamic). Neuropathy was assessed by nerve conduction velocity tests, Valk questionnaire, MNSI and light touch test. The subjects in the intervention group received 10 sessions of IPC and the control group received no physical intervention. The results from this study showed that applying IPC on the lower libs of neuropathic patients with T2D can reduce neuropathy signs and symptoms and associated imbalance. Also, IPC can decrease neuropathy severity measured by Valk and Michigan questionnaires in the intervention group. Improvement in balance was also seen in the intervention group.

Uzkeser and Karatay (2013) investigated the effect of intermittent pneumatic compression pumps on upper extremity impairments in breast cancer related lymphedema. Thirty-five patients with upper-extremity lymphedema following mastectomy with no history of physical therapy participated in this study. The participants were randomly split into 2 groups; a pneumatic compression group and a control group. The treatment of the IPC group (n=12) included skin care, manual lymph drainage, IPC, compression bandages and exercises. The control group went through the same program but without IPC. Both groups were treated 5 times a week for 3 weeks, for a total of 15 sessions. Results showed that there were no significant differences in the upper limbs ROM after the therapy or 1 month after completing the therapy. However,

there were significant improvements immediately after the therapy and 1 month after completing the therapy in both groups.

Labropoulos, et. al. (2005) measured the hemodynamic effects of IPC in patients with critical limb ischemia (CLI) in the systemic, muscular, and collateral circulation as well as in the foot skin blood flow. Twenty patients with CLI (mean age=74 years) were evaluated with duplex ultrasound scans and laser Doppler fluxmetry in the semi-erect position before, during and after IPC. One IPC cuff was applied on the foot and the other on the calf and inflated to 120 mmHg. The cuffs were applied for 3 seconds at three cycles. Flow volumes were measured in the popliteal, medial gastrocnemial and a genicular collateral artery. Skin blood flux was measured on the dorsum of the foot at the same time. There was a significant flow increase during the application of IPC in all three arteries compared with baseline values. There was a significant increase in skin blood flux also. After IPC treatment was over, blood flow returned to baseline.

Hanson, E., Stetter, K., Li, R., & Thomas, A. (2013) investigated intermittent pneumatic compression units as a recovery modality by evaluating its effectiveness in clearing blood lactate when compared to alternative recovery methods following a Wingate test. Twenty-one female student athletes, between the ages of 18 and 25, participated in this study. Following a standardized Wingate test, the subjects were randomized into three groups: passive (n=7), active (n=7) and IPC (n=7). Prior to testing, each subjects blood pressure and heart rate were obtained. Also, height, weight and resting blood lactate was measured. Following a one-minute, all out, bike sprint test, subjects immediately began their recovery process. Group 1 performed a passive long sit recovery where the participant sat with their hips at 90° of flexion and knees in full

extension. Group 2 performed an active recovery on a stationary bike at 40% HRR. Group 3 was placed in the IPC compression unit on the "recovery flush" setting with their hips at 90° flexion and knees extended. There was a statistically significant difference in BLa concentrations between the three groups, with most of the differences being between the passive and IPC groups. One reason the IPC may be better than passive is because the IPC mimics the muscle-venous pump.

Alternative Methods of Compression

Amah, Voicu, Bonnin & Kubis (2016) investigated whether forearm skin blood flow could be improved when a multiplayer pulsatile inflatable suit was applied at a low pressure to the lower limbs and abdomen. Twenty-four (12 men and 12 women), ages 18-65, were included in the study. All subjects did a pulsatile suit session, an acetylcholine iontophoresis test and a local cutaneous hyperthermia test. Systolic, diastolic and mean blood pressures and heart rate were measured at baseline and at the end of the pulsatile inflated suit procedure. For each subject, the entire study duration lasted 3 hours. This study showed that the pulsatile inflated suit is a reliable method to non-invasively improve endothelial function. A 20 minute session of 65 mmHg of the low pressure pulsatile suit was able to induce an increase in blood flow of the forearm skin without any adverse effect.

Bonetti, et. al. (2003) examined the effect of enhanced external counterpulsation on endothelial function. Twenty-three patients were involved in this study. All subjects had refractory angina. All patients underwent a standard 35-hour course of EECP (1 hour each day, for 5 days, over 7 weeks). Acute hemodynamic effects of EECP, measured as the peak diastolic-to-systolic pressure ratio, were monitored using conventional finger

plethysmography. Each session was scheduled at the same time each day to prevent possible effects of circadian variability. Reactive hyperemia-peripheral arterial tonometry (RH-PAT) measurements were done immediately before and after each treatment session 1, session 17 and session 35. RH-PAT was also measured one month after completion of EECP. All patients (n=23) completed the study, but only 18 patients returned for the 1 month follow up. EECP effectiveness ratio at the end of the EECP course did not differ from the beginning on treatment and EECP had no acute or chronic effect on heart rate or blood pressure in the patients studied. Before therapy, patients undergoing EECP had a significantly lower average RH-PAT index than healthy individuals. EECP led to an acute and significant increase in average RH-PAT index on all three monitored days and also at the one-month follow-up. The researchers concluded that EECP represents a valuable treatment option for CAD patients with refractory angina. Also, they concluded that EECP is associated with n acute improvement in peripheral endothelial function.

Nitric Oxide and Circulation

Kephart, et. al (2015) investigated whether a 60-minute bout of whole-leg, lower pressure external pneumatic compresssion altered select vascular, metabolic, antioxidant and inflammation related mRNA's. Ten college students were enrolled in this study (n=8 males, n= 2 females). Participants were already healthy, had no history of blood clotting and consumed no ergogenic nutritional supplements for at least 1 month prior to the study. On the day of testing, participants were to be fasted for 4 hours prior to the study. First, a percutaneous skeletal muscle biopsy was taken from the left vastus lateralis midway between the patella and iliac crest. The biopsy sample was frozen in liquid nitrogen and stored at -80°. The NormaTec was applied to the right leg for 60 minutes.

The target inflammation pressure was 70 mmHg. After the 60 minutes EPC, two separate skeletal muscle biopsies were obtained; one and 4 hours after EPC. The researchers found that a single bout of EPC upregulated PGC-1a mRNA expression and also alters eNOS protein and nitric oxide. eNOS mRNA increased by 44% 1 hour following EPC. This changed was followed by 36 and 55% increases in eNOS protein and NOx in skeletal muscle tissue samples 4 hours following EPC. They concluded that, at this amount of time or even longer, nitric oxide levels increase with EPC treatment.

Awata, et. al (2004) examined the endothelial nitric oxide (eNOS) gene polymorphisms to assess its possible association with diabetic retinopathy and macular edema. The study examined 226 T2D patients (age range 15-86 years) and 184 healthy patients (age range 18-47 years). BMI, height, weight, blood pressure, fasting HbA1c, cholesterol and triglycerides levels were measured before the study. All patients had a complete ophthalmological examination. The human eNOS gene consists of 26 exons. The researchers identified three polymorphisms of the eNOS gene. Among the 226 T2D patients, 109 had no evidence of retinopathy. There were no significant differences in genotypes and allele frequencies between any groups versus the DR patient results. eNOS polymorphisms were not associated with the presence of DR or with DR severity. Genotype and allele frequencies of the eNOS polymorphisms in 204 healthy subjects were not significantly different from the frequencies in the total T2D patients. This showed that eNOS polymorphisms were not associated with T2D itself. The study did suggest that the eNOS gene polymorphisms, T-786C in the promoter region and 27-bp repeat in intron 4 were associated with ME in patients with T2D.

Limb compression can potentially stimulate vasoactive substances caused by the increased sheer stress. Thomas, et. al. (2002) assessed the cardiovascular response to four limb compression and examined blood pressure, nitric oxide and prostacyclin levels. Twenty subjects were split into two groups; a CAD group and a healthy group. All subjects perform regular mild to moderate aerobic exercise 3-4 times/week. Prior to the start of the study, each subject completed health history, medical and activity questionnaires and also were instructed to avoid caffeine, aspirin and exercise the day of testing. Each subject performed 15 consecutive days of compression treatment. Each treatment session was 45 minutes long and on days 1 and 15, blood parameters were taken after the session. The results showed that acute compression treatment caused a significant decrease in nitric oxide and prostacyclin levels on both days, in both groups. The research also suggests that only one day of compression will lower NO levels.

Previous research suggests that nitric oxide is important in regulating glucose uptake during exercise in Type 2 diabetes. Richter & Hargreaves (2013) compared the effect of upper and lower body resisted exercise glycated hemoglobin and nitric oxide in Type 2 diabetics. Sixty type 2 diabetics, between the ages of 50 and 60, were selected to participate in either an upper or lower exercise program. The 6-minute walk test, glycated hemoglobin and nitric oxide values were obtained and analyzed before beginning the exercise program and after 3 months of the exercise program. Results showed that there was a significant increase in six-minute walk test and nitric oxide in both groups and a decrease in glycated hemoglobin in both groups. Group A, the upper body resistance group, showed more improvement in glycated hemoglobin and nitric oxide than Group B.

CHAPTER III

METHODS

Research Design

This is a causal-comparative research study. The independent variable is pneumatic compression and the dependent variables are inflammatory markers Interleukin 6 (IL-6) and C-reactive protein (CRP), HbA1C, glucose, Insulin, and nitric oxide. The study was delimited to participants diagnosed with type 2 diabetes mellitus.

Subjects. This study included 10 volunteer participants, five men and five women, with an age range between 48 & 66 (Table 1). All subjects have been clinically diagnosed with Type 2 diabetes mellitus. Participants were recruited through convenience sampling via flyers and word of mouth at Cleveland State University and within the Cleveland community.

Table 1 Subject Characteristics

Mean HbA1C	Mean Fasting Glucose	Mean Age
7.66 ± 1.87	151.75 ± 49.58	58.2 ± 7.21

All subjects signed an informed consent, approved by the Cleveland State Institutional Review Board for use of human participants, laying out all procedures, risks

and benefits. Subjects were educated on the use of the intermittent pneumatic compression (IPC) device and the FreeStyle Libre System (FSL) for measuring glucose.

Procedures. All participants were asked to maintain a normal daily routine throughout the study. Participants needed to be available for 2 days of pre and post testing and 3 days dedicated to 1-hour at home treatments (Table 2).

Table 2 Study Timeline

Control Day	Day 1	Days 2-4	Day 5
Home	**Human Perf. Lab**	**Home**	**Human Perf. Lab**
Blood Glucose Monitoring 15-minute Blood Glucose (FLS) 30-minute Blood Glucose (FLS) 45-minute Blood Glucose (FLS) 60-minute Blood Glucose (FLS) 70-minute Blood Glucose (FLS) 80-minute Blood Glucose (FLS) 90-minute Blood Glucose	Consent IPC and FLS Explanation 4-hour fast **Blood Sampling-Pre** Nitric Oxide, Insulin, Inflammatory Markers (IL-6 and CRP), HbA1C **Treatment (1 hour)** Pre-Blood Glucose (FLS) 15-minute Blood Glucose (FLS) 30-minute Blood Glucose (FLS) 45-minute Blood Glucose (FLS) 60-minute Blood Glucose (FLS) **Immediately Post Treatment** **Blood Sampling- Post** Nitric Oxide, Insulin, Inflammatory Markers (IL-6 and CRP) **Recovery (30 minutes)** 10-minute Blood Glucose (FLS) 20-minute Blood Glucose (FLS) 30-minute Blood Glucose (FLS)	**Pre-Treatment** Blood Glucose (FLS) **Treatment (1 hour)** 15-minute Blood Glucose (FLS) 30-minute Blood Glucose (FLS) 45-minute Blood Glucose (FLS) 60-minute Blood Glucose (FLS) **Recovery (30 minutes)** 10-minute Blood Glucose (FLS) 20-minute Blood Glucose (FLS) 30-minute Blood Glucose (FLS)	**Blood Sampling-Pre** Nitric Oxide, Insulin, Inflammatory Markers (IL-6 and CRP), HbA1C **Treatment (1 hour)** Pre-Blood Glucose (FLS) 15-minute Blood Glucose (FLS) 30-minute Blood Glucose (FLS) 45-minute Blood Glucose (FLS) 60-minute Blood Glucose (FLS) **Immediately Post Treatment** **Blood Sampling- Post** Nitric Oxide, Insulin, Inflammatory Markers (IL-6 and CRP) **Recovery** 10-minute Blood Glucose (FLS) 20-minute Blood Glucose (FLS) 30-minute Blood Glucose (FLS)

Prior to the start of the study, participants performed a Control Day which consists of an hour and a half of glucose monitoring using their Freestyle Libre System. For pre-testing, participants were asked to be fasted for 4 (four) hours. Pre-tests included a 5 ML blood sample obtained via aseptic technique from the antecubital vein taken at rest and immediately post treatment. Only phlebotomy-trained individuals performed blood draws. The blood draw site was thoroughly cleaned and sanitized with alcohol. Only sterile blood collection items were used. All blood supply items used during the blood collection were discarded in accordance with biohazard regulations. The blood samples clotted for a minimum of 30 minutes and were then spun down using a high-speed centrifuge. The serum was drawn off and stored in a -80 degree C freezer until analyzed using commercially available ELISA kits for insulin, nitric oxide, and inflammatory markers Interleukin 6 (IL-6) and C-reactive protein (CRP). An additional blood sample was taken by a finger prick and analyzed for HbA1C using the Alere Cholestech LDX analyzer.

Immediately after pre-testing, participants stayed in the human performance lab to do their first 1-hour intermittent pneumatic compression (IPC) treatment using the NormaTec Pulse recovery system. This specific pneumatic compression device is boot-like and fits snug around each participants legs. The NormaTec is divided into sections or cells (cells 1-5) that fit around a certain part of the leg. The first cell (cell 1) is located at the foot and continues to cell 5 which tops off at the thigh. All subjects received treatment at the same intensity setting of 10. According to previous research, this is the recommended setting for best results. The NormaTec uses pulse massage patterns and three different techniques (pulsing, gradients and distal release) that are important for

movement of fluid, forced pressure and circulatory flow. Participants received three logs to keep track of their medications and glucose levels. During the IPC treatment, participants recorded their glucose reading every 15 minutes using the FreeStyle Libre System (FSL) prescribed by their doctor. The FLS is a continuous glucose monitoring system that comes with a sensor and a handheld device. The sensor is the size of a quarter and uses a thin, flexible filament inserted right under the skin. It works by using wired enzyme technology and direct signaling. The sensor is worn for up to 14 days on the upper arm and is waterproof. The handheld device continuously measures glucose every minute and internally stores glucose readings. The participants placed the handheld device on the sensor and it immediately gave them a painless reading. Immediately after treatment, post testing was done in the same manner as the pre testing analyzing for the same variables. Recovery glucose readings were also recorded every 10 minutes using the FLS system for 30 minutes.

At home, participants were asked to fast for 4 hours prior to treatment. At home treatment was done for 3 consecutive days. Before at-home testing began, a baseline glucose reading was obtained and recorded using the FLS. During their 1-hour treatment, participants kept track of their glucose levels using the FLS to record blood glucose levels every 15 minutes during treatment and every 10 minutes post treatment for 30 minutes.

On day 5, participants returned to the human performance lab to do their last day of treatment. Day 5 followed the same procedures as day 1.

Data Analysis. Descriptive statistics were obtained. The repeated measures ANOVA, and inferential statistic, were used to assess treatment differences due to pneumatic compression on inflammation and glucose regulation. SPSS (version 25) was used for all analyses with .05 used as the level of significance.

CHAPTER IV

RESULTS AND DISCUSSION

Ten subjects with Type 2 Diabetes participated in the study to determine whether Intermittent Pneumatic Compression (IPC) acutely improves inflammation and glucose regulation. The subjects performed a total of five IPC treatments; two in the Human Performance Laboratory and three at home. Serum samples were obtained pre- and post-treatment on the 1st and 5th day in the laboratory to analyze insulin, Interleukin 6 (IL-6), C-reactive Protein (CRP) and Nitric Oxide (NO). A finger prick was performed on day one in the laboratory to obtain HbA1C. Repeated measures ANOVA was used to compare pre- and post-treatment glucose regulation and inflammation markers. Each graph shown shows +/- the standard error for each outcome.

Results from the repeated measures ANOVA showed no main effect on control day, lab and home values for average blood glucose every 15 minutes for total treatment time, or total session time. However, there was a significant change in blood glucose levels during recovery. In terms of inflammatory markers, there were no significant changes observed for Nitrate, IL-6, CRP or insulin.

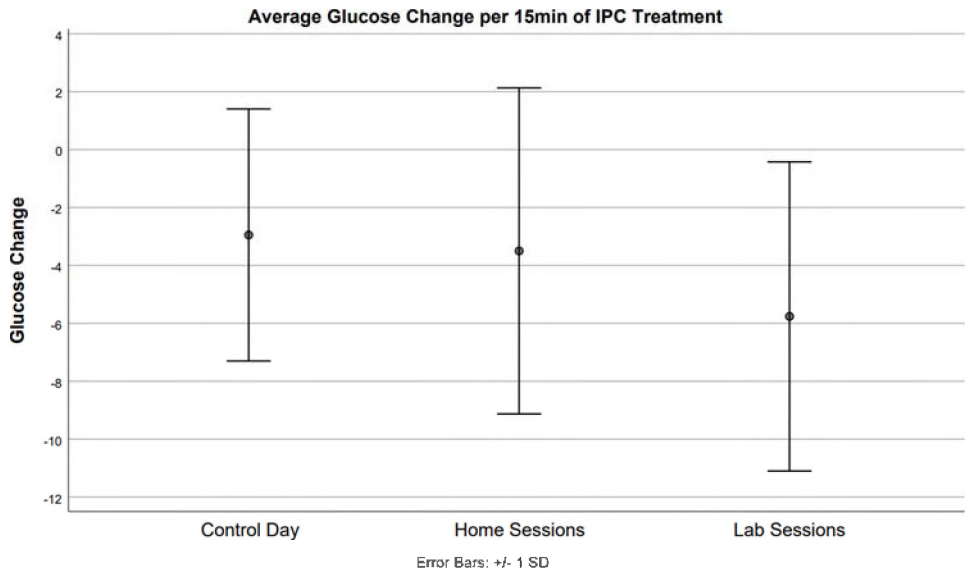


Figure 1: Glucose Change per 15-minute of Treatment by Location

Figure 1 shows the average change of blood glucose per 15 minutes of treatment. The biggest decrease in blood glucose levels were observed in the lab setting (-5.76 ± 5.34), followed by the home setting (-3.5 ± 5.63) and then the control setting (-2.95 ± 4.35). No significant changes were observed.

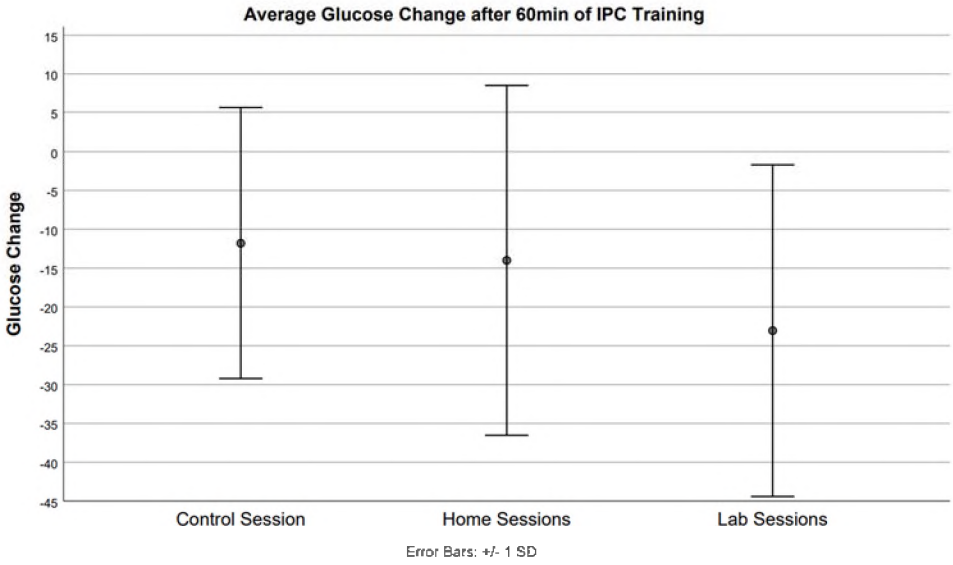
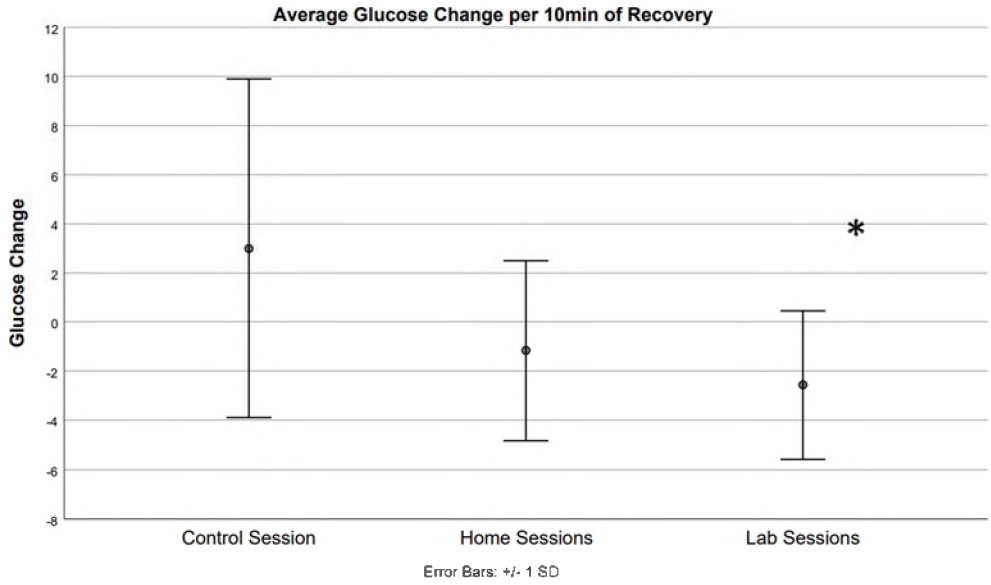


Figure 2: Glucose Change per 60-minute of Treatment by Location

Figure 2 shows the average change of blood glucose per 60 minutes of treatment. The biggest decrease in blood glucose levels were observed in the lab setting (-23.05 ± 21.35), followed by the home setting (-14.0 ± 22.52) and control setting (-11.8 ± 17.41) showing the smallest decrease in blood glucose levels. No significant changes were observed.



** Indicates significance ($p < 0.05$)*

Figure 3: Glucose Change per 10-minute Recovery by Location

Figure 3 shows the average change of blood glucose per 10-minute recovery. There was a significant decrease ($p = 0.03$) in blood glucose levels in the lab setting (-2.60 ± 3.01). A slight decrease in blood sugar levels were seen in the home setting (-1.17 ± 3.67), however a slight increase in blood glucose levels were present in the control setting (3.0 ± 6.90).

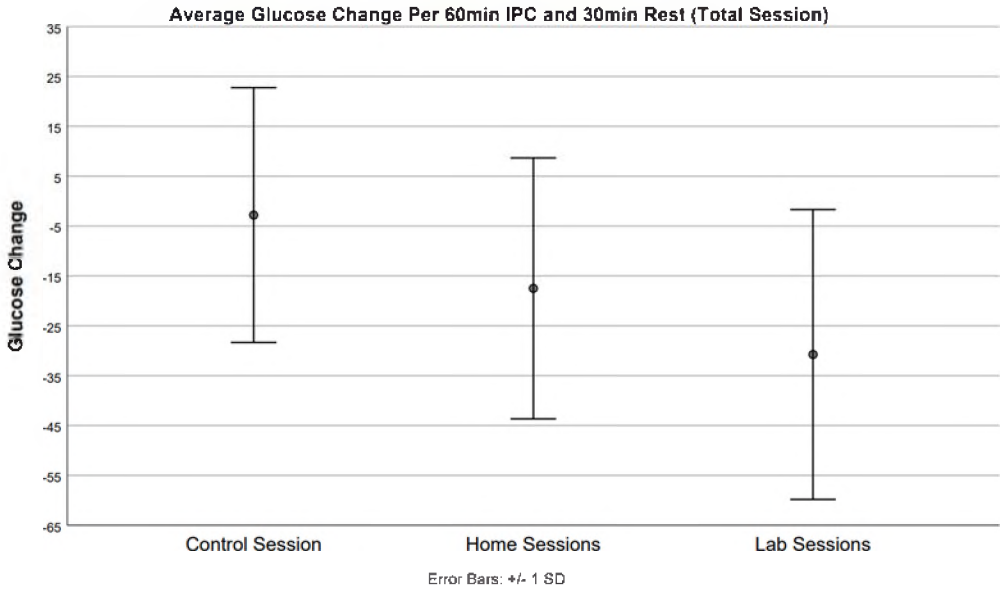


Figure 4: Glucose Change per Total Session by Location

Figure 4 shows the average change of blood glucose levels per total session (treatment + recovery). The biggest decrease in blood glucose levels to be in the lab setting (-30.75 ± 29.06), followed by the home setting (-17.5 ± 26.16) and then the control setting (-2.8 ± 25.55). No significant changes were observed.

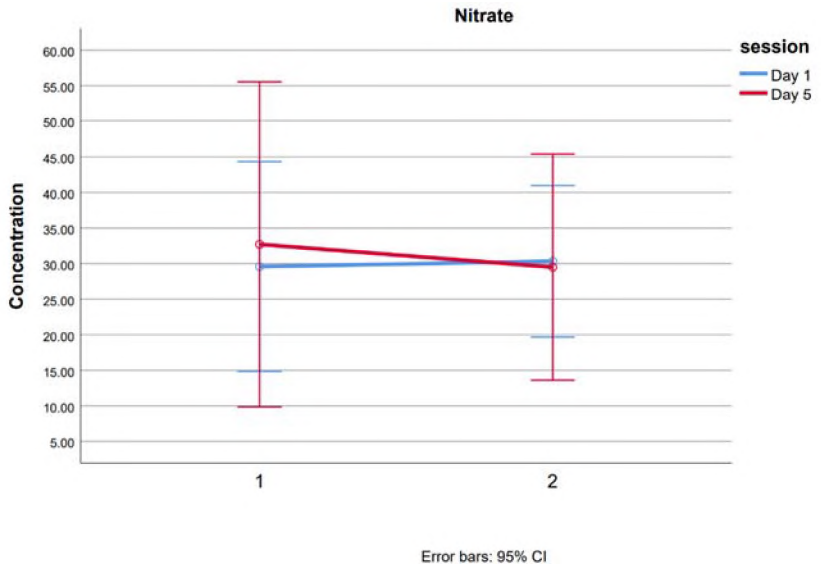


Figure 5: Pre/Post Nitrate Concentration Change (Day 1 vs. Day 5)

Figure 5 shows the change in Nitrate concentration for pre and post testing on days 1 and 5. There was no significant difference between the two testing days. The pre to post change on day 1 showed little to no change. However there was a slight, but non significant decrease in Nitrate concentration from pre to post on day 5. Nitrate concentration values on day 5 were very similar.

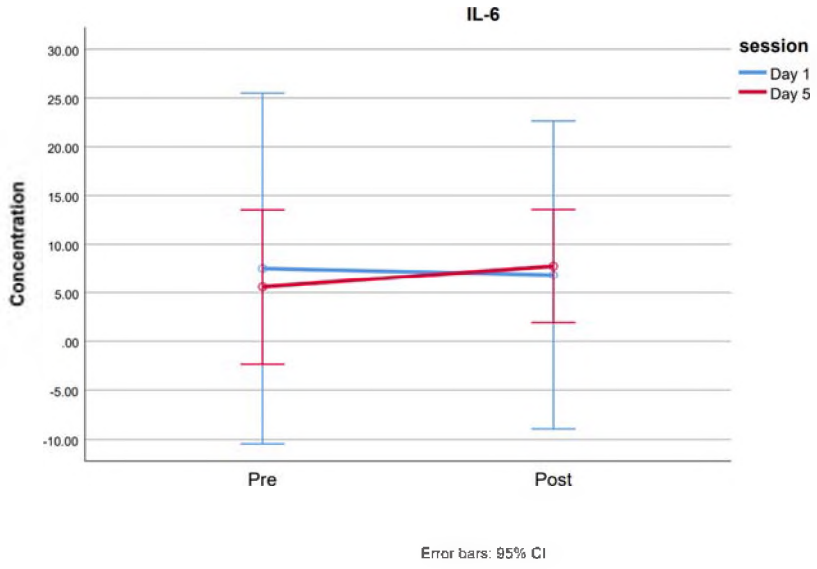


Figure 6: Pre/Post Interleukin-6 (IL-6) Concentration Change (Day 1 vs Day 5)

Figure 6 shows the change in IL-6 concentration for pre and post testing on days 1 and 5. There was no significant difference between the two testing days. On day 1, there was a slight, but nonsignificant decrease from pre to post testing but on day 5 there was a slight increase in IL-6 values from pre to post testing.

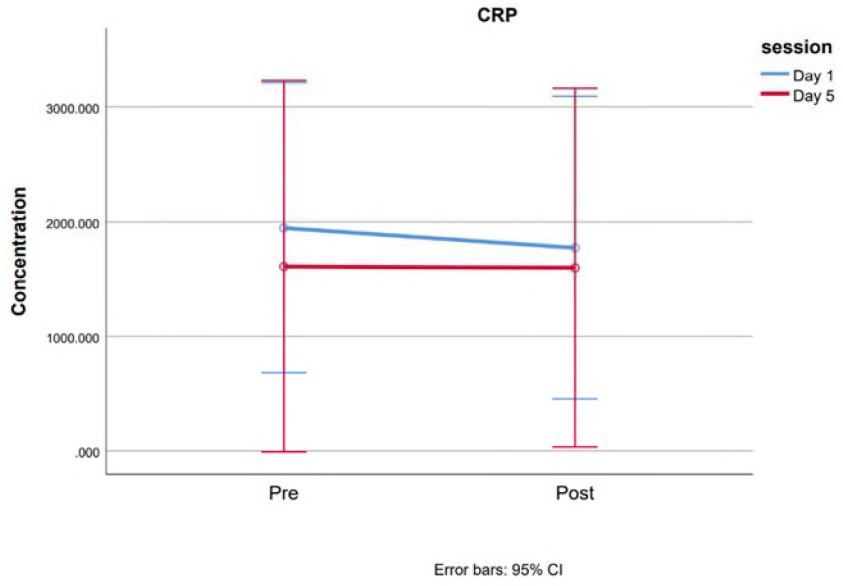


Figure 7: Pre/Post C-Reactive Protein (CRP) Concentration Change (Day 1 vs. Day 5)

Figure 7 shows the change in CRP concentration for pre and post testing on days 1 and 5. Day 1 showed a slight decrease in CRP values from pre to post testing, but there was no significant change. Day 5 showed little to no change from pre to post testing.

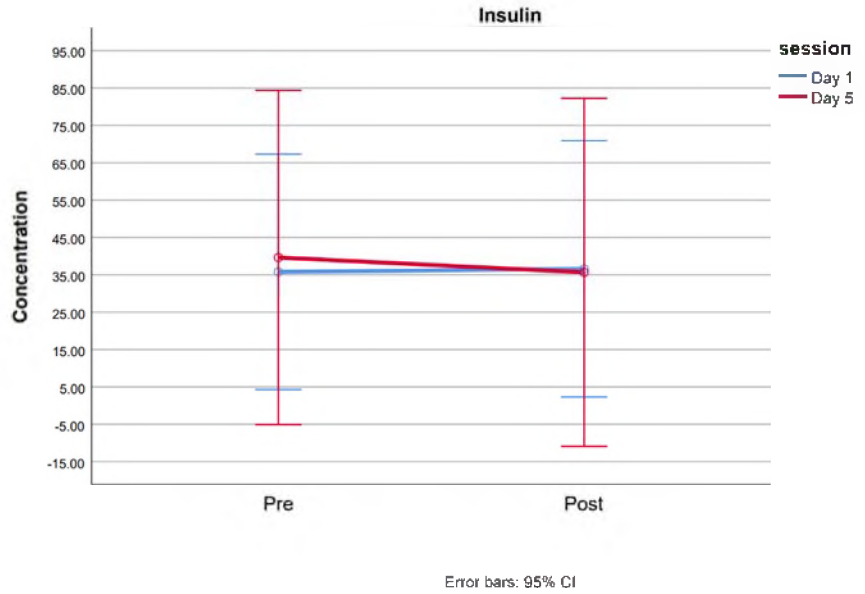


Figure 8: Pre/Post Insulin Concentration Change (Day 1 vs. Day 5)

Figure 8 shows the change in Insulin concentration for pre and post testing on days 1 and 5. Day 1 showed a small increase from pre to post testing. However day 5 showed a nonsignificant increase. Post testing Insulin values were very similar on day 5 compared to day 1.

Discussion

Blood glucose, inflammatory markers IL-6 and CRP, nitric oxide and insulin were measured and analyzed. No significant changes were observed throughout factors, except in the recovery stage of treatment.

Inflammation. Little to no change was observed in IL-6, CRP or nitric oxide concentration levels from day 1-5. Slight decreases in IL-6 and CRP pretest values on day 1 and 5 may suggest acute IPC treatments have a positive effect on mortality and cardiovascular outcomes. Singh-Manoux, et. al (2013) examined whether CRP and IL-6 were good predictors of mortality. As a result of their study, IL-6 may be the best indicator of long-term health status and CRP & IL-6 are the most important predictors of mortality. Decreasing certain inflammatory markers can potentially slow down the development of characteristics associated with Type 2 Diabetes. Malencia, et. al. (2017) concluded that the concentration of many inflammatory markers, at an acute phase, correlates with the development of obesity, insulin resistance and complications in Type 2 Diabetics. Inflammatory markers (CRP and IL-6) are significantly higher in Type 2 Diabetics (Malencia, et. al., 2017). High inflammatory levels can affect an individuals endothelium and cause harmful damage. Bonnetti, et. al (2003) examined the effects of EECP on endothelial function in individuals with coronary artery disease. Along with the results from the present study, Bonnetti's study showed that compression therapy may

help individuals stay away from any further cardiovascular complications because of the positive outcomes from decreased inflammatory markers. Although these outcomes were not significant, these findings could potentially aid future research.

Overall, there was no change in Nitrate/Nitrite concentration levels from day 1-5. Although a slight increase in pre-test Nitrate values was observed from day 1-5, there were no significant changes. This present study was one of the first to examine the association between nitric oxide and intermittent pneumatic compression. Kephart, et. al (2015) examined the effect of a 60-minute whole leg EPC treatment on inflammation mRNA's and nitric oxide. Although there was a slight increase in pre-test Nitrate values, there was a small, non-significant, decrease in Nitrate levels on Day 5. These results go along with a previous study by Thomas, et. al (2002). This study examined the cardiovascular and nitric oxide response to four limp compression. Although subjects performed 15 days of treatment, the results showed a significant decrease in nitric oxide levels in just one day. Because of the hypothesized increased vasodilation response to compression treatments, one would assume that nitric oxide levels would increase. More research needs to be conducted to assess the effect of IPC on nitric oxide levels, along with other inflammatory markers.

Glucose Regulation. Compared to the subjects' blood glucose levels on their control days (no treatment), blood glucose levels decreased during treatment and total sessions on both the home and lab days. There was a significant decrease in blood glucose levels during the recovery portion of the study on the lab days. Insulin concentration showed little to no change over the 5-day study. Effect sizes for all variables of blood glucose showed there was a small effect on acute IPC treatment on

Type 2 Diabetes. Labpropolous et. al (2005) showed that IPC treatment may lead to an increase in blood flow. The decrease in blood glucose levels and small decline in insulin levels could be attributed to the increased blood flow from the IPC treatment. The significant decrease in blood glucose levels during the recovery phase (after treatment) shows that IPC treatment has positive effects on blood glucose levels even after treatment has been completed. The effect size of .432 indicates a small/medium relationship between IPC and treatment of Type 2 Diabetes. Although more research needs to be done at the acute level, IPC treatment may help decrease insulin in newly diagnosed patients and increase insulin levels in patients that have had T2D for some time now. Insulin becomes a tricky subject when dealing with Type 2 Diabetics. How long they have had diabetes plays a huge role in Insulin sensitivity. Lim et. al (2011) explains beta cell burnout, which occurs overtime with Type 2 Diabetes. When individuals are first diagnosed, insulin levels are high because their bodies are trying to reduce blood glucose. Seeing a decrease in insulin indicated improves insulin sensitivity. On the other hand, individuals that have had diabetes for most of their life show low insulin levels because of beta cell damage. Seeing an increase in insulin in this population would indicate improved beta cell function. IPC can also lead to a decrease in blood glucose levels and can possibly be a supplement to medication for Type 2 Diabetics.

Setting. Blood glucose levels decreased during 60-minute treatment and 30-minute recovery on home and lab days. There was a significant decrease in blood glucose levels during recovery in the lab setting. Overall, blood glucose levels decreased more in the lab setting than the home and control settings and more in the home setting than the control. On the control day, subjects received no treatment and picked and hour and a

half to monitor and record their blood sugar using the CGMS. Blood glucose levels most likely remained unchanged on this day because we did not control for any outside factors and no treatment was received. Blood glucose levels most likely decreased more in the lab setting because the study was more controlled. We took their glucose for them every 15 minutes during the treatment and every 10 minutes during recovery. We kept a time so we knew exactly what time the subjects were at the whole time. When the subjects were at home doing their IPC treatment, they may have been just been watching the clock and not using a stopwatch. Subjects were also seen at the same time on days one and five. At home, subjects were asked to fast for four hours prior to treatment, but they could choose any time of the day to conduct treatment. Because of these factors, one can assume that blood glucose levels decreased more in the lab setting because of the controlled environment.

CHAPTER V

SUMMARY AND CONCLUSION

Previous research has been conducted on intermittent pneumatic compression devices and their effects on inflammation and glucose regulation in Type 2 Diabetics. The hypothesis was supported due to the significant decrease in blood glucose levels in the recovery portion of the treatment. The results also showed a slight decrease in blood glucose levels in other portions of the treatment, along with a small increase in pre-test Nitrate levels.

Current research shows that inflammation and glucose levels may be influenced by compression treatments. Inflammation, especially in individuals with Type 2 Diabetes, can lead to detrimental effects on the body such as obesity, cardiovascular risks and damage to the endothelium. Previous research shows many positive effects from compression treatments on blood flow, blood sugar, neuropathy issues and characteristics that go along with type 2 diabetes. An increase in blood flow may lead to decreases in inflammatory markers CRP and IL-6, a decrease in blood sugar and insulin levels and an increase in Nitrate levels in just 5 days, which shows that IPC treatment and other compression treatments can possibly lead to advances in the medical field for Type 2 Diabetes. Adding IPC to a patient's treatment plan could possible help individuals with Type 2 Diabetes cut back on or replace certain medications. More research needs to be

done on how effective the acute use of IPC treatments are for individuals with Type 2 Diabetes.

CHAPTER VI

APPLICATION, LIMITATIONS AND FUTURE RESEARCH RECCOMENDATIONS

Application

Today, individuals with Type 2 Diabetes are told to take medication and make a lifestyle change to better their condition. If further research is done using compression treatments to assess the positive effects it has on Type 2 Diabetes, then this may be an alternative or supplement to certain medications. The use of IPC devices is currently being used in the medical field to help with cardiovascular disease, ulcers and thrombosis. Although more research needs to be done on how this affects individuals with Type 2 Diabetes, this could potentially be an advance in the medical world for controlling Type 2 Diabetes.

Limitations

Limitations of the study were identified as followed:

1. The study contained a small sample size (N = 10).
2. Although a medication log was kept, medications were not controlled.
3. Diet and exercise was not controlled, which could have led to different outcomes for the variables measured.

4. The time that subjects completed treatment at home was not controlled, which could have also led to the variables measured.

5. Height, weight and BMI were not measured

Future Research Recommendations

1. A larger sample size would be recommended for any future research done on this subject.

2. Controlling for diet and exercise may help with any factors that may have influenced the variables examined.

3. Having the subjects perform treatment at home, at the same time every day, may help with improving consistency of future research and with any limiting factors that may have influenced outcomes.

REFERENCES

Amah, G., Voicu, S., Bonnin, P., & Kubis, B. (2016). Low-pressure sequential compression of lower limbs enhances forearm skin blood flow. *Clin Invest Med, 39*(6), 204-212.

Awata, T. et. al. (2004). Endothelial nitric oxide synthase gene is associated with diabetic macular edema in type 2 diabetes. *Diabetes Care, 27*(9), 2184-2190.

Bolinder, J., Antuna, R., Duijvestijen, P., Kroger, J. & Weitgasser, R. (2016). Novel glucose sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *The Lancet*, 388(10057), 2254-2263.

Boneetti, P. et. al. (2003). Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. *Journal of the American College of Cardiology, 41*(10), 1761-1768.

Campbell, P. J., Mandarino, L. J., & Gerich, J. E. (1988). Quantification of the relative impairment in actions of insulin on hepatic glucose production and peripheral glucose uptake in non-insulin-dependent diabetes mellitus. *Metabolism, 37*(1), 15 21.

Carey M, Kehlenbrink S, Hawkins M. (2013). Evidence for central regulation of glucose metabolism. *J Biol Chem*, *288*, 34981–34988.

Chen, A., Frangos, S., Kilaru, S., & Sumpio, B. (2001). Intermittent pneumatic compression devices – Physiological mechanisms of action. *European Journal of Vascular and Endovascular Surgery, 21*(5), 383-392.

Devkota, B. (2014). *C-reactive protein. Medscape drugs & diseases.* Retrieved from https://labtestsonline.org/tests/c-reactive-protein-crp

Elgazzar, S., Elasaadany, O., Obaya, H., & Helmy, M. (2019). Effect of Upper Versus Lower Limbs Resisted Exercise on Nitric Oxide Levels in Diabetic Patients; Type 2. *The Egyptian Journal of Hospital Medicine, 74*(8), 1799-1803.

Gross, T. M., & Mastrototaro, J. J. (2000). Efficacy and Reliability of the Continuous Glucose Monitoring System. *Diabetes Technology & Therapeutics*, *2*(supplement 1), 19–26.

Haffner, S.M. (2006). The metabolic syndrome; inflammation, diabetes mellitus, and cardiovascular disease. *American Journal of Cardiology*. 97(1); 3-11.

Hanson, E., Stetter, K., Li, R., & Thomas, A. (2013). An intermittent pneumatic compression device reduces blood lactate concentrations more effectively than passive recovery after wingate testing. *Journal of Athletic Enhancement, 2*(3), 1 4.

Herder, C., Carstensen, M., & Ouwens, D. M. (2013). Anti-inflammatory cytokines and risk of type 2 diabetes. *Diabetes, Obesity and Metabolism, 15*(S3), 39-50.

Kaneto, H., Fujii, J., Seo, H. G., Suzuki, K., Matsuko, T. A., Masahiro, N., ... & Taniguchi, N. (1995). Apoptotic cell death triggered by nitric oxide in pancreatic β-cells. *Diabetes*, *44*(7), 733-738.

Kaptoge, S. et. al. (2010). C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *The Lancet, 375*, 132-140.

Kephart, W. et. al. (2015). A single bout of whole-leg, peristaltic pulse external pneumatic compression upregulates PGC-1α mRNA and endothelial nitric oxide sythase protein in human skeletal muscle tissue. *Experimental Physiology, 100*(7), 852-864.

Labropoulos, N., et. al. (2005). Hemodynamic effects of pneumatic compression in patients with critical limb ischemia. *Society for Clinical Vascular Surgery, 42(*4), 710-716.

Malencia, M. et. al. (2017). Importance of inflammatory markers and IL-6 for diagnosis and follow up of patients with type 2 diabetes mellitus. *Med Glas, 14*(2), 169-175.

Martin, J. S., & Braith, R. W. (2012). Anti-inflammatory effects of enhanced external counterpulsation in subjects with abnormal glucose tolerance. *Applied Physiology, Nutrition, and Metabolism, 37*(6), 1251-1255.

Mihai, V.C., et. al. (2018). Insulin resistance (IR) in patients with type 2 diabetes mellitus. Identifying predictor of insulin resistance and establishing a correlation between insulin resistance and cardiovascular risk. *Internal Medicine, 15(*2), 7-15.

Nolan, C. J., Damm, P., & Prentki, M. (2011). Type 2 diabetes across generations. Pathophysiology to prevention and management. *The Lancet, 378*(9786), 169 181.

Richter, E.A., & Hargreaves, M. (2013). Exercise, GLUT4 and skeletal muscle glucose uptake.Physiol. Rev., 93:993-1017.

Salek, S., Bahrpeyma, F., & Mohajeri-Tehrani, M.R. (2015) Intermittent pneumatic compression therapy improves functional and dynamic balance and neuropathy severity in neuropathic patients with type 2 diabetes. *Int J Diabetes Dev Ctries, 35*(3), 439-448.

Shoelson, S. E., Lee, J., & Goldfine, A. B. (2006). Inflammation and insulin resistance. *The Journal of Clinical Investigation*, *116*(7), 1793-1801.

Singh-Manoux, A., Shipley, M. J., Bell, J. A., Canonico, M., Elbaz, A., & Kivimäki, M. (2016). Association between inflammatory biomarkers and all-cause, cardiovascular and cancer related mortality. *Canadian Medical Association Journal, 189*(10), 384-390.

Stumvoll, M., Goldstein, B. J., & van Haeften, T. W. (2005). Type 2 diabetes: principles of pathogenesis and therapy. *The Lancet*, *365*(9467), 1333-1346.

Suh, DC., Choi, IS., Plauschinat, C., Kwon, J., & Baron, M. (2010). Impact of comorbid conditions and race/ethnicity on glycemic control among US population with type 2 diabetes. *Diabetes Complications, 24,* 382-391.

Tanenberg, R., et.al. (2004). Use of the Continuous Glucose Monitoring System to Guide Therapy in Patients With Insulin-Treated Diabetes: A Randomized Controlled Trial. *Mayo Clinic Proceedings*, *79*(12), 1521–1526.

Thomas, T., et.al. (2002). Does four limb compression mimic the effects of exercise? *Journal of the American Society of Exercise Physiologists, 5*(1), 32-41.

Uzkeser, H., Karatay, S., Erdemci, B., Koc, M., & Senel, K. (2013). Efficacy of manual lymphatic drainage and intermittent pneumatic compression pump use in the treatment of lymphedema after mastectomy: A randomized controlled trial. *Breast Cancer, 22*(3), 300-307.

Wang, C. et. al. (2012). Glucose fluctuations in subjects with normal glucose tolerance, impaired glucose regulation and newly diagnosed type 2 diabetes mellitus. *Clinical Endocrinology, 76,* 810-815.

Weyer, C., Bogardug, C., Mott, D., Pratley, R. (2011). The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *Journal of Clinical Investigation, 104*(6), 787-794.

Wilcox G. (2005). Insulin and insulin resistance. *The Clinical biochemist. Reviews*, *26*(2), 19-39.

Appendix A

Informed Consent

Acute Effects of Pneumatic Compression on Inflammation and Glucose Regulation in Type 2 Diabetics

Introduction and Purpose

This study is being completed by students and faculty from Cleveland State University's Health and Human Performance Department. This research is being undertaken by Dr. Kenneth Sparks, Dr. Emily Kullman, Dr. Doug Wajda (Cleveland State), Dr. Van Iterson (Cleveland Clinic) and graduate researcher Madison Mariola.

The purpose of this study is to determine the acute effects of intermittent pneumatic compression (IPC) on endothelial function and metabolism in type 2 diabetics.

The NormaTec will be the main device used in this study. It is a popular IPC that was designed to enhance blood flow and speed recovery in athletes. Previous research has shown that type 2 diabetics have lower than average blood circulation. This research aims to identify if acute use of the NormaTec device will have any immediate circulation effects and effects on glucose regulation in individuals with type 2 diabetes.

Procedures

You will be asked to respond to the medical history questionnaire before the start of the study. You will need to be available for one (1) control day and a total of 5 consecutive testing days (first and last day- testing will be performed in the Human Performance lab, 3 days at home). You will also be asked to keep your typical diet, exercise and medication routine the same. At home treatments will consist of 1 hour treatments and monitoring of glucose levels using the FreeStyle Libre System. Baseline blood samples will be taken on day one and again on the last day. A small blood sample will be obtained for lipid profiles and HbA1c. Plasma samples will be obtained to measure nitric oxide, insulin and IL-6.

Risks and Discomforts

Risks associated with this study include discomfort while using the NormaTec device and giving blood samples. Only qualified personnel will be administering the NormaTec treatment and drawing blood.

Benefits

There is no direct benefit or medical benefit and it is not to be a medical treatment while participating in this study nor should it be used in place of regular medical care. You will receive a Freestyle Libre System that will be taken care for you by the department. This research study can help also future researchers in finding a valid glucose regulation treatment.

Confidentiality

All efforts will be made to keep your data confidential, any data and information obtained during your participation will not be disclosed to anyone without your consent. Your data will only be used as group data without any identification of participant's names.

Participation

Your participation in this study is completely voluntary. You may withdraw from the study at any time, without penalty or consequence.

Questions about the procedures used in this research are welcomed. If you have any doubts or questions, please contact Dr. Kenneth Sparks at 216-687-4831.

Subject Acknowledgment

I have read and understand this consent form or it has been read to me and I understand it. The procedures, purposes and known discomforts, risks and benefits of this research have been explained to me. I have had a chance to ask questions and they have been answered sufficiently. I am 18 years or older and I voluntarily consent to participate in this study and I have been given a copy of this consent form.

I understand that if I have any questions about my rights as a research subject I can contact the Cleveland State University Institutional Review Board at 216-687-3630.

Participant Signature: _____ Date: _____

Witness Signature: _____ Date: _____

Appendix B

Medication Log

Name of Medication	Dosage	Quantity	Time of Day Taken

Appendix C

Glucose Log

Please use this log to record glucose readings every 15 minutes during your one (1) hour treatment and every ten (10) minutes during your 30-minute recovery period.

Control Day

IPC 15 minutes: _____ R 10 minutes: _____

IPC 30 minutes: _____ R 20 minutes: _____

IPC 45 minutes: _____ R 30 minutes: _____

IPC 60 minutes: _____

Day 1

IPC 15 minutes: _____ R 10 minutes: _____

IPC 30 minutes: _____ R 20 minutes: _____

IPC 45 minutes: _____ R 30 minutes: _____

IPC 60 minutes: _____

Day 2

IPC 15 minutes: _____ R 10 minutes: _____

IPC 30 minutes: _____ R 20 minutes: _____

IPC 45 minutes: _____ R 30 minutes: _____

IPC 60 minutes: _____

Day 3

IPC 15 minutes: _____ R 10 minutes: _____

IPC 30 minutes: _____ R 20 minutes: _____

IPC 45 minutes: _____ R 30 minutes: _____

IPC 60 minutes: _____

Day 4

IPC 15 minutes: _____ R 10 minutes: _____

IPC 30 minutes: _____ R 20 minutes: _____

IPC 45 minutes: _____ R 30 minutes: _____

IPC 60 minutes: _____

Day 5

IPC 15 minutes: _____ R 10 minutes: _____

IPC 30 minutes: _____ R 20 minutes: _____

IPC 45 minutes: _____ R 30 minutes: _____

IPC 60 minutes: _____

APPENDIX D

From: system@cayuse424.com <system@cayuse424.com>
Sent: Friday, April 12, 2019 1:43 PM
To: Kenneth E Sparks
Cc: Cayuse IRB
Subject: IRB-FY2015-69 - Modification approved

April 12, 2019

Dear Professor Kenneth Sparks,

I am writing In response to your study IRB-FY2015-69, *Effect of Intermittent Pneumatic Compression (IPC) on Endothelial Function and Metabolism in Type 2 Diabetes*, as acknowledgement of modifications to previously approved protocol. Please consider this email notice of the Approval for the requested modification to your Cayuse IRB Submission.

Investigator request to modify previously approved CSU IRB Submission #FY2015-69 as follows:
"The modifications are looking at the acute effect of intermittent pneumatic compression instead of chronic effect. The subjects will only do five days of treatment instead of 35 days. They will monitor their blood sugars every 15 minutes during treatment using a glucose reader and every 10 minutes after treatment for 30 minutes of recovery. Blood sugars will be monitored using the Free style Libre system that uses a reader held over an electrode which would not require multiple finger sticks. We will also measure lactic acid with a finger stick. The researchers are changing to include Dr. Erik van Iterson from the Cleveland Clinic and student Madison Mariola."
.....has been granted.

DO NOT REPLY TO THIS EMAIL. IF YOU WISH TO CONTACT US, PLEASE SEND AN EMAIL MESSAGE TO cayuseirb@csuohio.edu.

Sincerely,

Mary Jane Karpinski
IRB Analyst
Cleveland State University
Sponsored Programs and Research Services
m.karpinski2@csuohio.edu
216-687-3624