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THE POTENTIAL IMPACT OF CHEMOTHERAPEUTICS ON CALF VENOUS COMPLIANCE

Cooper M. Springfield
Southern Illinois University Carbondale, reddog.cooper@siu.edu

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By
Cooper McCarthy Springfield
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A Research Paper
Submitted in Partial Fulfillment of the Requirements for the
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There is evidence that arterial compliance can be lower in an individual who has undergone chemotherapy, but to date it has not been investigated as to whether the same is true for venous compliance. Investigate differences in the venous compliance in cancer survivors and healthy individuals. Twenty participants, 10 of whom were cancer survivors (CS=63.2 ± 6.7yrs), while the remaining 10 were healthy individuals (C=60.2 ± 6.7yrs) underwent submaximal graded exercise tests and assessment of calf venous compliance. Utilizing venous occlusion plethysmography, calf venous compliance was determined in both groups as the first derivative of the pressure-volume relation during cuff pressure reduction. Body mass (CS=73.5 $\pm$ 14.8 kg, C=82.3 $\pm$ 15.5 kg); height (CS=165.1 $\pm$ 7.9 cm, C=170.4 $\pm$ 14.8 cm); VO2 peak (CS=34.7 $\pm$ 9.6 $ml \cdot kg^{-1} \cdot \mathrm{min}^{-1}$, C=40.9 $\pm$ 9.8 $ml \cdot kg^{-1} \cdot \mathrm{min}^{-1}$); and resting blood pressures were not significantly different between the groups. Resting heart rate was (CS=76 $\pm$ 8.2 bpm, C=67.9 $\pm$ 8.9 bpm; $\rho < 0.05$) was significantly greater in cancer survivors. There were no differences in calf venous compliance, capacitance or capillary filtration volumes between the sexes. Results from this study indicate venous compliance is not different among cancer survivors who have received neuro-toxic or cardio-toxic chemotherapeutics and healthy individuals.

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CHAPTER 1

INTRODUCTION

Vascular compliance is a term used to describe the ability of the blood vessel wall to expand and contract passively with changes in pressure. Seventy percent of total blood volume in humans can be located within the distensible veins upon standing (orthostatic pressure) or experiencing lower body negative pressure (LBNP) (Freeman, Wieling, Benditt, Axelrod, & Benarroch, 2011; Gelman, 2008. Skoog , Zachrisson , Lindenberger, Ekman, Ewerman, & Lanne, 2014; Lida, et al., 2011). The translocation of blood that occurs in the lower extremities in response to orthostatic changes elicits reflex responses (increase in heart rate and peripheral arterial resistance) that allow us to maintain venous return, blood pressure and cerebral perfusion (Freeman, Wieling, Benditt, Axelrod, & Benarroch, 2011; Hernandez, et al., 2004; Mosqueda-Garcia, Furlan, Tank, & Fernandez-Violante, 2000).

Many pathophysiological conditions have been associated with irregular arterial compliance, such as hypertension, diabetes and venous insufficiency (Delaney, Young, DiSabatino, Stillabower, & Farquhar, 2008; Goulopoulou, Deruisseau, Carhart Jr., & Kanaley, 2012). One such morbidity, brought on by the sympathetic nervous systems' improper control of arterial compliance, is known as diastolic heart failure. This condition is characterized by a stiff left ventricle with decreased compliance and impaired relaxation. Vasoconstriction, or increased resistance to blood flow, can be stimulated by the sympathetic nervous system (SNS) which produces a hormonal cascade resulting in the secretion of catecholamines (especially epinephrine and norepinephrine). Under ordinary circumstances, the autonomic nervous system keeps arterial vessel tone balanced. However, if the SNS is stimulating the smooth muscles of the arterial vessels for prolonged periods of time, complications can arise.

Autonomic nervous system impairment, or neuropathy, is a nervous system disorder affecting the control of involuntary functions, including digestion, heart rate, blood pressure, and perspiration. Neuropathy has already been shown to result from the treatment of various chemotherapeutics currently being used in oncologic medicine. The research team led by Adams was recently able to successfully link neuropathy found in cancer patients who had received four rounds of chemotherapy to aberrant blood pressure changes and maladaptive orthostatic responses (Adams, 2015). If patients are showing signs of poor orthostatic responses as a result of autonomic nervous system dysfunction, the veins of the lower body are likely being affected in some manner. That said, how the venous compliance of the lower limbs is being affected by this phenomenon is still unknown.

Various cancer therapeutics, such as anthracyclines, are associated with increased risk for cardiovascular complications (Criscitiello, Metzger-Filho, & Saini, 2012; Chen, Xu, & Li, 2011; Hedhli , 2011; Volkova & Russell, 2011; ETH, 2009). Anthracyclines are dose-dependent in how they initiate cardio-toxicity (Cortes-Funtes & Coronado, 2007). This cardio-toxicity often contributes to cardiomyopathy and congestive heart failure, which is associated with the drugs' interaction with iron, and production of potent reactive oxygen species (Jones , Stoner, Brown, Baldi, & McLaren, 2013). Furthermore, among women who have survived breast cancer, mortality due to cardiovascular disease is more common than cancer-related death, (Jones , Stoner, Brown, Baldi, & McLaren, 2013). Of these women, 45% of all cardiovascular-related deaths in individuals over the age of 55 years were attributed to coronary artery disease, which triggers a decline in arterial compliance resulting in higher peripheral blood pressure, among other effects (Jones , Stoner, Brown, Baldi, & McLaren, 2013). A peak in mortality due to circulatory system disorders appears at approximately 5 years' post-diagnosis. This may be

indicative of the fact that the impact of chemotherapeutics on the circulatory system may be chronic rather than acute (Jones , Stoner, Brown, Baldi, & McLaren, 2013). Doxorubicin, for example, is a cardio-toxic drug that can lower the hearts pumping capability, hindering the hearts' total stroke volume. Such a result from taking chemotherapeutics could cause abnormalities in heart rate, which if left unsupervised, could lead to future cardiac events. This coupled with the possibility of having higher arterial stiffness could force heart rate to increase during exercise.

Other chemotherapeutics like paclitaxel can inhibit the growth of smooth muscle cells found in blood vessel walls (Axel, et al., 1997). Inhibiting the overall proliferation and migration of vascular smooth muscle cells could be a detriment to the healthy development and function of the vascular system, taking place over a period of time rather than an immediate change in vasculature health. Furthermore, disruption of endothelial cell health could further disrupt the processes carried out by the smooth muscle cells (Francois et al, 2006).

With the vascular smooth muscle cells composing a portion of the extracellular matrix, this proliferation, inhibition, or exacerbation could upset the overall conformation of the matrix. With elastin being the structure that allows for the majority of venous passive elasticity, which also resides in the extracellular matrix, it is possible that changes to the vascular smooth muscle cells and disruption of the endothelial cells could impact the function of elastin (Francois et al, 2006). With too little a ratio of smooth muscle to elastin, such a matrix composition could result in a vessel that is overly elastic and subject to greater expansion during pressure increases. The end result of this compositional change would most likely be blood pooling. Conversely, if a matrix has an excessive quantity of smooth muscle, the vessel may be overly resistant to expansion and contraction, increasing blood pressure. Both composition situations would prove

to be damaging to the overall status of the cancer survivors' health. This warrants a greater understanding to what extent the compositional changes occur, which would allow for the necessary medical actions to take place to assure no further damage is done to the integrity of the vessel walls; thus, preventing further circulation stresses.

If damage is done to the venous endothelial lining, the scarring and healing process produces tissue that is often limited in its compliance or elasticity (Huang et al, 2014). The pathophysiology of cancer survivors developing various cardiovascular conditions is still not a fully understood sequence of events. Specifically, the venous compliance changes associated with chemotherapeutic treatment require further study. Researchers have yet to examine whether any changes occur in venous compliance due to chemotherapeutics (Jones, Stoner, Brown, Baldi, & McLaren, 2013; Makari-Judson, Braun, Jerry, & Mertens, 2014). The exact chemotherapeutics being examined were determined by the impact the individual medications had on each participants' body: anthracyclines such as Doxorubicin (Adriamycin), Epirubicin, Idarubicin, Daunorubicin, and medications that exhibit neurotoxic affects much like Paclitaxel, and Docetaxel (Taxotere). The study called for both men and women to account for the differences in circulatory characteristics, as women are more susceptible to orthostatic stress than men are (Lindenberger & Lanne, 2007; Lindenberger & Lanne, 2007).

The purpose of this study was to use venous occlusive plethysmography (VOP) to measure the venous compliance within the calves of cancer survivors who had undergone specific chemotherapy and determine if the measures were markedly different than the compliance of apparently healthy individuals who are age and physical activity-matched.

We hypothesize that venous compliance would be consistently lower in cancer survivors than the compliance of similar healthy individuals. The independent variables within the study

were the healthy participants and the treatments taken by the cancer survivors while the dependent variable were the resultant venous compliance of both groups. The results found within this study should be generalizable to cancer patients of varying physical activity levels who have taken similar chemotherapeutics to those received by the participants of the study.

CHAPTER 2

METHODS

Participants

The sample size consisted of 20 participants, 10 (8 females, 2 males) of whom have gone through chemotherapy (Cancer Survivor=CS), and 10 (5 females, 5 males) healthy participants (Control=C) who were low risk asymptomatic men and women who have ≤1 CVD (Cardiovascular disease) risk factor and have not been diagnosed with cancer. The age of the cancer survivors (63.2 ± 6.7yrs) was similar to that of the age of the healthy participants (60.2 ± 6.7yrs). Physical activity engagement for the CS group was also closely matched to the physical activity engagement of the C group. Exclusion criteria included patients who have received surgery rather than drug therapy and participants with a family history of heart and circulation events/disease.

Screening

Participants were given a medical history and physical activity history form to complete. The participants' blood pressure, heart rate, body composition, height, and weight were then measured. The participants were told to refrain from consuming any caffeine, alcohol, and/or dietary supplements 24 hours prior to testing.

Venous Occlusion Plethysmography (VOP)

Changes in calf volume were evaluated with strain-gauge plethysmography. The instrument (Hokanson: EC5R-Plethysmograph) was used to measure volume changes (ml 100 ml^{-1}) of a limb by measuring the circumference. Data was recorded in a temperature-controlled room (24-26 ℃). Participants were placed in a supine position where they were put through an acclimation period of 15 minutes with their right leg or dominant leg slightly elevated with

support located at the ankle. Maximal calf size was measured, as the strain gauge was placed on this location. A 22-cm-wide thigh cuff was placed on the thigh proximal to the knee on the left leg. The cuff was then inflated to 60 mmHg using a cuff inflator (Hokanson: E20 Rapid Cuff Inflator, AG101 Cuff Inflator Air Source). After 8 minutes of venous stasis, cuff pressure was reduced by 1 mmHg per second in a linear fashion (Halliwill J. M., 1999).

Calf Venous Compliance

Calf venous compliance (C_{calf}, ml 100 ml^{-1} $mmHg^{-1}$) was calculated from the pressure-volume relationship during the deflation phase. Data below 10 mmHg was excluded from analysis due to the potentially less reliable relation between cuff pressure and venous pressure at that level (Halliwill, Lawler , Eickhoff, Joyner, & Mulvagh, 1998; Halliwill, Minson, & Joyner, 1998; Skoog , Zachrisson , Lindenberger, Ekman, Ewerman, & Lanne, 2014). Venous pressure-volume curves were non-linear, with a steeper slope at greater compliance and a flatter slope at lower compliance. Characteristics of the pressure-volume curves from deflation readings were described as a quadratic regression equation (Halliwill, Lawler , Eickhoff, Joyner, & Mulvagh, 1998; Halliwill, Minson, & Joyner, 1998):

$$\Delta\text{Volume} = \beta_0 + \beta_1 \times (\text{cuff pressure} + \beta_2 \times (\text{cuff Pressure})\text{^}2$$

β_0 was the y-intercept and together β_1 and β_2 were characteristics of the slope generated by the pressure-volume curve. C_{calf} was defined as the first derivative of the pressure-volume curve, creating a linear pressure-compliance curve:

$$C_{calf} = \beta_1 + 2 \times \beta_2 \times (\text{cuff Pressure})$$

The slope of this curve equals the derivative of the pressure-compliance curve (slope = 2 $\times$ β_2) and the regression parameters β_1 and β_2 was used as estimates for C_{calf}. Use of a *t*-test

between the cancer survivors and the general population regarding typical venous compliance measurements were necessary to view any differences in compliance between the two groups.

Submaximal Fitness Assessment

Each participant completed his or her involvement with the study by performing a graded submaximal treadmill test to determine fitness level (Modified Bruce Protocol). Peak oxygen uptake (VO_2) was estimated in all participants using time to termination of a modified Bruce treadmill protocol. The Modified Bruce Protocol has 2 warmup stages, each of which lasting 3 minutes. The first was at a speed of 1.7 mph and a grade of 0%, while the second was at a speed of 1.7 mph and a grade of 5%. Each subsequent stage lasted 3 minutes and increased in grade and/or speed until the participant reached 65% of the difference between their age-predicted maximal heart rate and resting heart rate (Target heart rate). The test was terminated when the participant reached their THR or 12-13 on the RPE scale. The protocol is used most often in older individuals or those whose exercise capacity is limited by cardiac disease. Pre-exercise resting heart rate and blood pressure measurements were taken. Heart rate was measured using a Polar Heart Rate Monitor™. Blood pressure was measured manually using a pressure cuff on the upper arm. Heart rate and blood pressure was recorded during each stage. To minimize risks associated with a submaximal exercise test, the researcher (who was CPR certified) was constantly at the participants' side to help reduce risk. The researcher kept close track of heartrate, blood pressure, and the exertion levels perceived by the participant. If the participant felt uncomfortable or did not wish to continue the test due to feeling unsafe, the researcher immediately terminated the exercise test. The participant was also able to stop the test whenever they wished. Each participant continued to walk on the treadmill at a very low intensity until their heart rate had returned to resting levels. Participants had their fitness testing results given to

them upon completion of the testing. They were explained the importance of the test results as well as given a handout showing their results.

Analysis

The data gathered from the research was recorded on a Dell PC (Biopac Data Acquisition Software) which was then used for analysis. The resultant pressure-volume curves following the initial decrease in pressure were expressed by a quadratic regression equation[$\Delta LV=\beta1+\beta2*(\text{Cuff Pressure})+\beta2*(\text{Cuff Pressure})^2$]. The group-average regression parameters $\beta1$ and $\beta2$ were applied together as an estimate of compliance [Compliance=β1+2*β2*(Cuff Pressure)]. The initial derivative yields a linear pressure-compliance relationship and this slope was used to determine differences amongst participants who had gone through chemotherapy to those who had not.

The capacitance response was computed from the volume rise at the onset of cuff pressure to the line defined from the filtration slope between 3 and 8 minutes of cuff pressure application. Total capillary filtration during cuff pressure application was calculated from the rate of filtration (ml/min) times the time of the cuff pressure application (8 min). Total calf volume increase was the sum of the capacitance and net capillary filtration volumes.

Anthropometric and compliance (β's) variables were compared between cancer participants and healthy participants using an independent t-test (PASW 18). Statistical significance was set at $\rho<0.05$. All data are presented as means $\pm$ SD (pg. 11-12).

CHAPTER 3

RESULTS

Participants Characteristics

Anthropometric characteristics and resting cardiovascular variables of all participants are displayed in Table 1. The cancer survivors (63.2 $\pm$ 6.7 yrs) and healthy individuals (60.2 $\pm$ 6.7 yrs) did not vary significantly with respect to age. Body mass (CS=73.5 $\pm$ 14.8 kg, C=82.3 $\pm$ 15.5 kg); height (CS=165.1 $\pm$ 7.9 cm, C=170.4 $\pm$ 14.8 cm); VO2 peak (CS=34.7 $\pm$ 9.6 $ml \cdot kg^{-1} \cdot \mathrm{min}^{-1}$, C=40.9 $\pm$ 9.8 $ml \cdot kg^{-1} \cdot \mathrm{min}^{-1}$); calf volume (CS=3710 $\pm$ 810 ml, C=4540 $\pm$ 1510 ml); and resting blood pressures were not significantly different between the groups. Resting heart rate (CS=76 $\pm$ 8.2 bpm, C=67.9 $\pm$ 8.9 bpm; $\rho < 0.05$) was significantly greater in cancer survivors.

Table 1. *Anthropometric Data for all Participants*

Variable	Cancer	Healthy
Age, yr	63.2 ± 6.7	60.2 ± 6.7
Weight, kg	73.5 ± 14.8	82.3 ± 15.5
Height, cm	165.1 ± 7.9	170.4 ± 14.8
VO2peak, ml · kg $^{-1}$ · min^{-1}	34.7 ± 9.6	40.9 ± 9.8
SBP, mmHg	119.3 ± 15.4	131.1 ± 15.3
DBP, mmHg	75.5 ± 11.2	73.8 ± 8.9
HR, beats/min	76 ± 8.2	67.9 ± 8.9*
Calf Volume, ml	3710 ± 810	4540 ± 1510

Values are mean and SD from 20 participants, 10 cancer survivors ad 10 healthy individuals; VO2peak, peak oxygen uptake; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; * p <0.05 vs. cancer survivor.

Venous compliance

The regression parameters calculated for calf venous compliance β0, β1, β2 (mean $\pm$ SD) are presented in Table 2 (Below). There were no significant differences in calf pressure volume

curves (Figure 1, Table 2) or venous compliance slopes (Figure 2, Table 2). Capacitance and capillary filtration volumes (Figure 3) also did not differ between cancer survivors and healthy individuals.

Table 2. *Calf Volume pressure volume regression equations*

Group	Cancer
Calf	$\Delta LV = 1.308 \pm 1.097 + 0.083 \pm 0.066 * (Cuff) + -0.0006 \pm 0.0013 * (cuff)^2$
	Healthy
Calf	$\Delta LV = 1.147 \pm 0.843 + 0.07 \pm 0.049 * (Cuff) + -0.0005 \pm 0.001 * (cuff)^2$

ΔLV, change in limb volume; CP, cuff pressure
[Δlimb volume = βo + β1 * (cuff pressure) + β2 (cuff pressure)²]

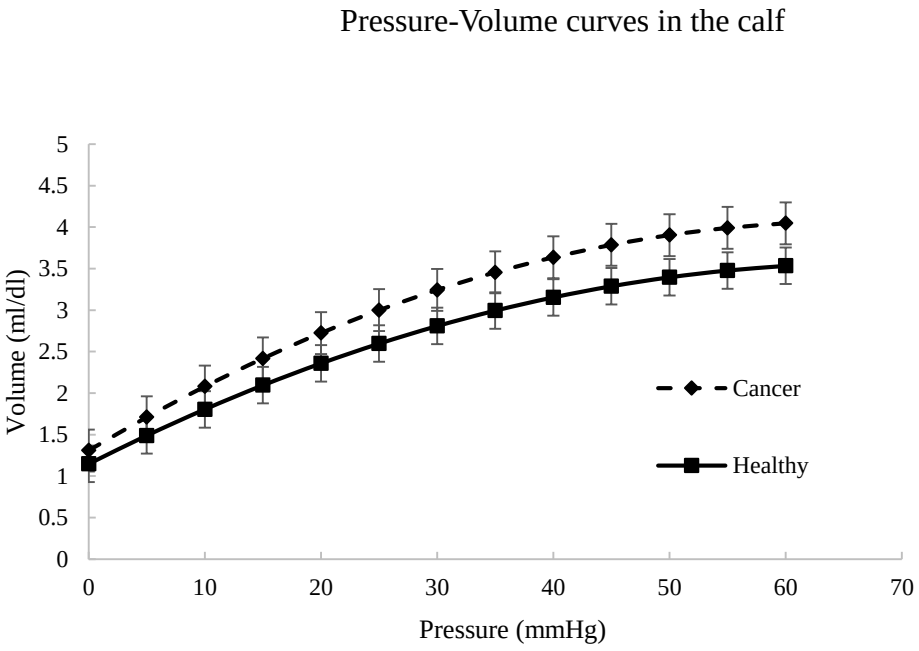

Figure 1. Pressure-Volume relationship. Data points are mean ± SEM

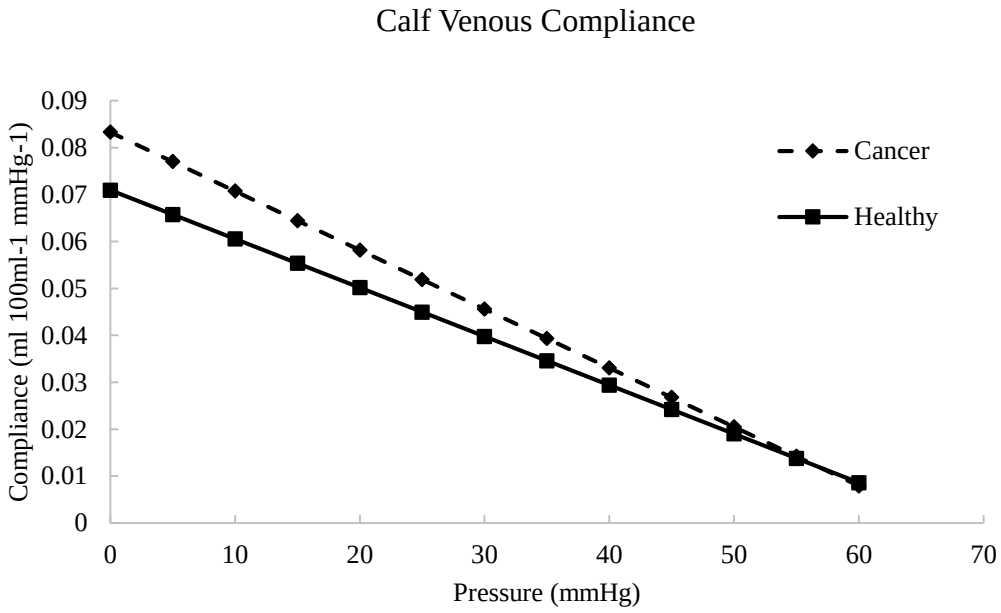

Figure 2.

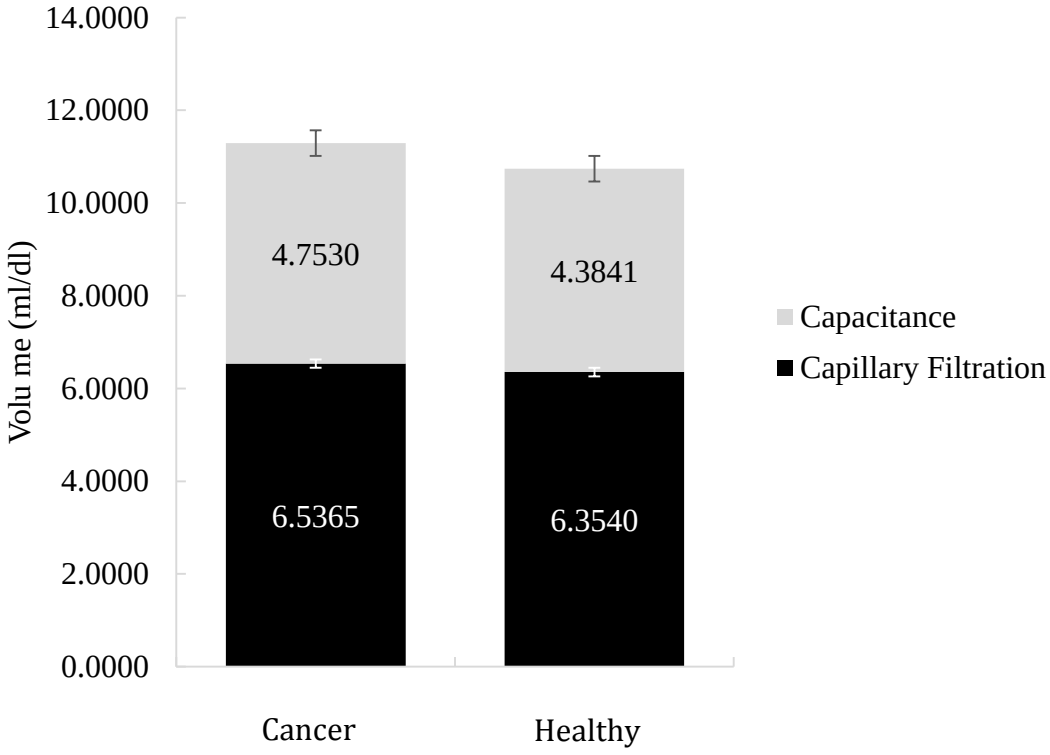

Figure 3. Capacitance and Capillary Filtration. Data points are mean ± SEM

CHAPTER 4

DISCUSSION

The purpose of this investigation was to determine if differences in venous compliance exist between cancer survivors who have received cardio-toxic or neuro-toxic chemotherapeutics and that of healthy age and physical activity-matched individuals. The primary finding of the current investigation revealed that our collected data indicated no differences in venous compliance between cancer survivors and healthy individuals. Therefore, the data do not support our hypothesis that cancer survivors who have received cardio-toxic or neuro-toxic chemotherapeutics would have lower compliance compared to healthy individuals.

Potential Mechanisms

Venous and arterial compliance is known to decline with age and improve with chronic exercise (Monahan K.D., 2001; Monahan, 2004; Hernandez, et al., 2004). The mechanisms eliciting such changes in compliance of vessels are potentially related to either structural changes in the ratio of elastin to collagen within the vessel wall, or to alterations in sympathetically mediated vascular tone. In relation to the venous wall, it is observed that aging decreases compliance through compositional changes to the elastin-to-collagen ratio (Bouissou, 1991), which makes it the most likely contributor to decreases in venous compliance. Noted arterial compliance changes in relation to the use neuro-toxic chemotherapeutics are more likely elicited by improper stimulation of sympathetic hormones inducing the smooth muscle of the vessel to constrict. The lack of smooth muscle found in the veins indicates that such sympathetic stimulation would not severly change venous compliance in an individual taking such chemotherapeutics. This further indicates that any potential changes in venous compliance are

related to compositional changes of the elastin-to-collagen ratio rather than sympathetic activation.

While the present study did not show any differences between the two groups, it is possible that any potential decreases in venous compliance that may be caused by chemotherapeutics in the CS group would be negated by an active lifestyle. One study comparing individuals with less physically active peers revealed venous compliance was 50% greater in more fit young and older groups (Hernandez, et al., 2004). The participants used in the present study were part of an exercise program in which exercise takes place at least two days out of the week. Each participant has been apart of the program for greater than year. It has been observed that older individuals who participate in at least 6 months of exercise training generated enough stimulus to elicit significant improvements in calf venous compliance. Longer durations of training may elicit greater changes in calf venous compliance. One study observed the venous compliance of older individuals who had been running for at least 2 years and found their compliance to be 70-120% higher than their sedentary peers (Monahan K.D., 2001).

There are a number of limitations that require consideration when reviewing the results of this investigation. First, in using venous occlusion plethysmography it is assumed that venous pressure is equal to venous collecting cuff pressure. We feel that the eight-minute collection cuff period was a sufficient enough duration for us to meet the assumption that collecting cuff pressure is equal to venous pressure; However, this was not directly assessed. Second, with our study only having evaluated older males and females of a particular physical engagement level who have undergone chemotherapy, our results cannot be generalized to all populations. There is a potential for cancer patients of differing physical engagement levels to repond differently.

CHAPTER 5

CONCLUSION

Results from this study indicate venous compliance is not different among cancer survivors who have received neuro-toxic or cardio-toxic chemotherapeutics and healthy individuals. Any compliance variations that may exist in persons treated with particular chemotherapeutics are not found in an older population that is physically active for 6 months or greater. Regardless of having a significantly higher resting heart-rate, cancer survivors had similar venous characteristics in their lower extremities as healthy individuals.

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VITA

Graduate School
Southern Illinois University

Cooper Springfield

Cmspringfi@gmail.com

Southern Illinois University Carbondale
Bachelor of Education, Kinesiology, May 2014

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