Increased arterial stiffness and reduced cardiovagal baroreflex sensitivity with anti-cancer chemotherapy

by

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Abstract

Background – Chemotherapy-induced left ventricular cardiotoxicity is associated with many cancer treatments; however, what is less known is how these treatments affect vascular health and autonomic control of blood pressure. Arterial stiffness and cardiovagal baroreflex sensitivity (BRS) are indicators of cardiovascular health and may provide insight into the adverse effects of anti-cancer chemotherapy. Therefore, the primary aims of the present study were to evaluate carotid artery stiffness and arterial BRS in cancer patients currently being treated with adjuvant chemotherapy.

Methods – We performed a cross-sectional, case-control study involving 9 cancer patients and 9 age- and sex-matched controls. Carotid artery stiffness was assess via 2D ultrasonography. Cardiovagal BRS was assessed from the spontaneous changes in beat-to-beat time series of R-R interval and systolic blood pressure via the cross correlation technique.

Results – Our findings indicated a significant decrease in cardiovagal BRS in cancer patients compared to controls (4.7 ± 0.6 vs 9.2 ± 1.7 msec mmHg^{-1} respectively, $P = 0.02$). Carotid artery β-Stiffness was significantly higher in the cancer patients compared to control participants (9.2 ± 1.2 vs 6.6 ± 0.74 U respectively, $P = 0.05$).

Conclusions – These data suggest that anti-cancer chemotherapy elicits significant decreases in the autonomic control of blood pressure and arterial stiffness, leaving cancer survivors with an increased risk of future cardiovascular disease.

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Acknowledgements

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Dedication

This project is dedicated to Jonathan Paul Frye and Edith Kay Billhimer. Cancer is a disease that doesn't discriminate, it just takes and it takes. You two know this from first-hand experience, and I never forget that. Every patient I met I saw you two in their eyes. You inspire me to serve them as I would serve you. I love you guys.

Chapter 1 -   Introduction

Anti-cancer chemotherapy is a common treatment option for numerous types of cancer that, while successful in terms of cancer survival, is associated with both acute and chronic cardiotoxicity (23, 25, 57). As such, anti-cancer chemotherapy is associated with increased cardiovascular disease risk, with cardiovascular disease being the second leading cause of mortality in breast cancer survivors (25, 57). While chemotherapy-induced left ventricular cardiotoxicity is well established (9, 29), certain types of chemotherapy have been linked to vascular abnormalities (38, 57), peripheral neuropathy (54, 7, 50), autonomic dysfunction (23, 50), and increased arterial stiffness (5, 11, 41). While current practices rely on traditional cardiovascular risk factors (46) to assess cardiovascular health, new methods of evaluating integrative cardiovascular function in cancer patients will provide additional insight into the early cardiotoxic effects of chemotherapy.

The arterial baroreflex is a tonically active feedback control system that is critical in the beat-to-beat regulation of arterial blood pressure by indirectly detecting changes in blood pressure via mechanoreceptors located in the walls of the carotid arteries and the aorta (44). This information is integrated in the nucleus tractus solitarius of the medulla and used to mediate both parasympathetic and sympathetic signaling to the heart and peripheral vasculature (32, 58). Recently, decreases in arterial baroreflex sensitivity (BRS) have been shown to occur with healthy aging (22, 37, 44), hypertension (22, 35), and during heart failure (47). Moreover, decreases in BRS have been identified as an independent risk factor for both acute and chronic cardiovascular problems, including increased morbidity and mortality (33, 47). Evidence suggests that these decreases in BRS observed in these populations could be due, in part, to a

stiffening of the carotid arteries (12, 43, 44). Increased arterial stiffness will decrease the magnitude of distention for a given increase in arterial pressure, thus decreasing the mechanical deformation of the baroreceptors (43). Therefore, any condition that alters the visioelestic characteristic of the vessel wall and the extravascular elements that connect it to the mechanosensitive nerve endings will potentially alter arterial baroreflex activity. Stiffening of the large arteries is present following chemotherapeutic cancer treatment (5, 11, 26, 41). Miza-Stec et al. (41) demonstrated in middle aged women that decreased arterial compliance and increased arterial stiffness are present within six months following chemotherapeutic treatment for breast cancer. Similarly, Chaosuwannakit et al. (11) also showed a significant increase in arterial stiffening over only a four month period following chemotherapy, but included a broader range of cancer patients (e.g., breast, lymphoma, or leukemia) into their study.

Despite these reported increases in arterial stiffness it is currently unknown if arterial BRS is decreased in cancer patients currently undergoing chemotherapy and if this is associated with increases in arterial stiffness. Therefore, the primary aims of the present study were to evaluate carotid artery stiffness and arterial BRS in cancer patients currently being treated with adjuvant chemotherapy. We hypothesized that cancer patients receiving chemotherapy would experience decreased arterial BRS and increased arterial stiffness when compared to age and sex matched healthy subjects.

Chapter 2 -   Methods

Participants

This study utilized a cross-sectional, matched case-control design with 8 patients diagnosed with cancer recruited from local oncology clinics. At the time of the study all patients were currently being treated with chemotherapy or a combination of chemotherapy and radiation as confirmed by their current oncologist/family practitioner (Table 1). Information on surgery was not obtained. Patients had been treated for cancer for an average of 4 months (range 1-13 months). Control group participants were matched for sex and age to individuals in the cancer group. Exclusion criteria for groups included; history of smoking, current smoker, diabetes, cardiovascular or cardiorespiratory diseases, and had received prior treatment for cancer. Current level of physical activity was determined using the International Physical Activity Questionnaire (47). Informed consent was obtained from all individuals included in the study according the Kansas State University (Manhattan, KS) Institutional Review Board for Research Involving Human Subjects requirements.

Experimental Design

The experiments were performed during a single session in a temperature-controlled clinical environment (~20-22°C), at least 4 hours after last meal and last caffeinated beverage, and > 12 hours after strenuous physical activity. The participant was placed in the supine position and allowed to rest for 5-10 minutes. Following this rest period the participant was instrumented for continuous beat-by-beat blood pressure and heart rate measurements. At least 10 minutes of resting baseline data were recorded during spontaneous breathing to assess

spontaneous cardiovagal BRS. Subsequently, ultrasonography of the common carotid artery was performed for the assessment of carotid artery stiffness.

Experimental Measurements

Systolic (SBP), diastolic (DBP), mean arterial pressure (MAP), and heart rate (HR) were measured on a beat-by-beat basis via a calibrated finger photoplethysmography system (Finometer Pro; Finapress Medical Systems, Amsterdam, The Netherlands). Brachial artery blood pressure was measured by an automated sphygmomanometer (Finometer Pro) and used to calibrate the reconstructed arterial pressure waveform via a "return-to-flow" procedure. In all instances, arterial pressure recordings were performed at heart level.

Spontaneous cardiovagal BRS was evaluated by examining the beat-to-beat time series of R-R interval and SBP via the cross correlation technique as previously described (45). Briefly, 10 second windows of simultaneous R-R interval and SBP were spline interpolated and resampled at one second intervals and used to identify arterial baroreflex sequences were identified as sequences of consecutive beats where R-R interval and SBP changed in the same direction. The slope between R-R interval and SBP was recorded as a BRS estimate if the $r^2 \geq$ 0.8 and was significant at $P \geq 0.01$. The biggest advantage of this method of BRS is that it provides a larger sampling size than other sequential methods, while having half the estimation variance (45).

Local cross-sectional carotid artery diameter was measured with a commercial 2D ultrasound system via a high-resolution phased-array transducer operating at 10M Hz and simultaneous ECG recordings. This system allows for sequential measurements of arterial wall motion across several cardiac cycles. Each participant had the left carotid artery imaged for a

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single 15 second interval while at rest with the transducer placed proximal to the carotid bifurcation. Maximal (i.e., end-systolic) and minimal (i.e., end-diastolic) luminal diameter were time aligned with photoplethysmography blood pressure measurements obtained during acquisition of the carotid artery measurements. These measures allowed for the calculation of mechanical strain and stiffness of the carotid artery (19, 22). For our various calculations, the following abbreviations will be used; carotid systolic diameter (CSD), carotid diastolic diameter (CDD), and carotid pulse pressure (CPP).

β-Stiffness was calculated as:

$$Ln\ (SBP/DBP)/((CSD - CDD)/CDD)$$

Carotid Artery cross-sectional compliance was calculated as:

$$\pi \times ((2 \times CDD) \times (CSD - CDD)) + (CSD - CDD)^2)/4 \times CPP$$

Statistics

Data were entered into SPSS 21 for analysis. Paired *t*-tests were used to identify differences between the control and cancer groups for all measured outcomes as previously described for matched case-control studies (65). Linear regression analysis and Pearson product moment correlations were used to evaluate the relationship between BRS and β-stiffness. All results are expressed as mean ± standard error. Differences were considered statistically significant when $P \leq 0.05$.

Table 1. *Cancer Patient Treatment Characteristics*

ID no.	Age (yrs)	Sex	Cancer Type	Chemotherapy treatment Cumulative dose to date	Months of Treatment
1	63	F	Pancreatic	-Fluorouracil 26000 mg -Oxaliplatin 680 mg -Xeloda 23000 mg	5
2	50	M	Non-Hodgkin's Lymphoma	-Bendamustine 1080 mg -Rituximab 2400 mg	2
3	39	F	Neuroendocrine Tumor	-Carboplatin 7150 mg -Etoposide 7200 mg -Fluorouracil 110,550 mg -Oxaliplatin 2200 mg	12
4	74	M	Non-Hodgkin's Lymphoma	-Cyclophosphamide 6000 mg -Doxorubicin 400 mg -Rituximab 3200 mg -Vincristine 8 mg	5
5	53	F	Breast	-Cyclophosphamide 4760 mg -Doxorubicin 476 mg -Paciltaxel 400 mg	5
6	54	F	Breast	-Doxorubicin 350 mg -Paclitaxel 350 mg	3
7	60	F	Breast	-Docetaxel 130 mg -Trastuzumab 367 mg	2
8	69	M	Prostate	-Docetaxel 150 mg	1

Chapter 3 - Results

General Characteristics

Participants receiving cancer treatment were diagnosed with breast cancer (n=3), lymphoma (n=2), pancreatic (n=1), or a metastatic tumor. Therapies included doxorubicin (n=3), fluorouracil (n=2), cyclophosphamide (n=2), docetaxel (n=2), carboplatin (n=2), rituximab (n=2), oxaliplatin (n=2), pacilltaxel (n=3), xeloda (n=1), bendamustine (n=1), etoposide (n=1), vincristine (n=1), trastuzumab (n=1). There were no significant differences in age, height, weight, and body mass index (BMI) between cancer patients and control participants. Resting SBP and DBP were also not different between groups. Of the cancer patients two (25%) were classified as inactive and six (75%) as minimally active. The control group was composed of one (13%) inactive and seven (87%) minimally active individuals.

Table 2 summarizes participant characteristics for both groups, while Table 3 summarizes carotid imaging results. Differences in carotid artery stiffness are illustrated in Figure 1. Carotid artery β-Stiffness was significantly higher in the cancer patients compared to control participants. However, carotid artery cross-sectional compliance was not significantly different between groups (P = 0.07). During the imaging of the carotid artery, arterial pulse pressure was not significantly different between groups. Individual and mean spontaneous cardiovagal BRS data are illustrated in Figure 2. Cancer patients had a significantly lower cardiac BRS compared to control participants (4.7 ± 0.8 vs 9.2 ± 1.7 msec mmHg^{-1} respectively, P = 0.017). A significant negative correlation was observed between carotid artery β-Stiffness and cardiovagal BRS (Figure 3, r = -0.61, P = 0.007).

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Table 2: Participant Characteristics

	Control (n = 8)	Cancer (n = 8)	P-value
Age, years	54 ± 3	58 ± 4	0.16
Sex, M/F	3/5	3/5	-
Height, cm	169.3 ± 2.4	168.1 ± 3.8	0.66
Weight, kg	70.3 ± 6.1	82.9 ± 9.1	0.27
BMI, kg/m^2	24.6 ± 1.5	29.1 ± 3.5	0.26
Systolic BP, mmHg	146 ± 5	142 ± 4	0.53
Diastolic BP, mmHg	79 ± 2	75 ± 3	0.28

Data are presented as mean $\pm$ SE; BMI, body mass index

Table 3. Carotid Artery Imaging

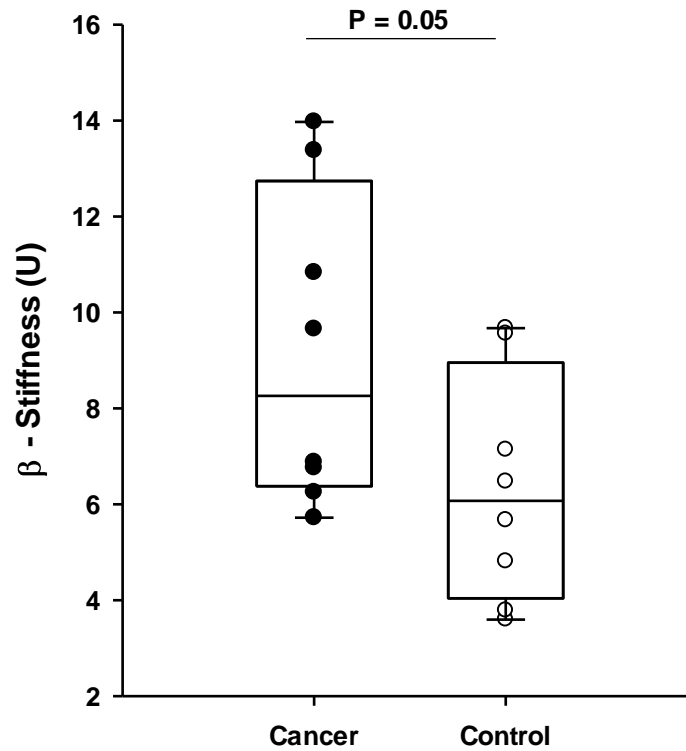|	Control (n = 8)	Cancer (n = 8)	P-value
Carotid artery diameter at end-diastole, cm	0.67 ± 0.04	0.72 ± 0.04	0.36
Pulse Pressure, mmHg	67 ± 3	67 ± 5	0.95
β-Stiffness Index	6.6 ± 0.7	9.2 ± 1.2	0.05

Data are presented as mean ± SE

***Figure 1-* β-stiffness box and whisker plot for cancer and control groups.** A significant increase in β-Stiffness was observed in the cancer patients compared to controls. Each data point is indicative of a single participant. Box plots summarize the distribution of values. The ends of the box are the 25th and 75th quartiles, with the center line indicating the median value. Whiskers indicate the 90th and 10th percentiles.

***Figure 2-* Cardiovagal baroreflex sensitivity box and whisker plot for cancer and control groups.** Baroreflex sensitivity was significantly decreased in the cancer group compared to controls. Each data point is indicative of a single participant. Box plots summarize the distribution of values. The ends of the box are the 25th and 75th quartiles, with the center line indicating the median value. Whiskers indicate the 90th and 10th percentiles.
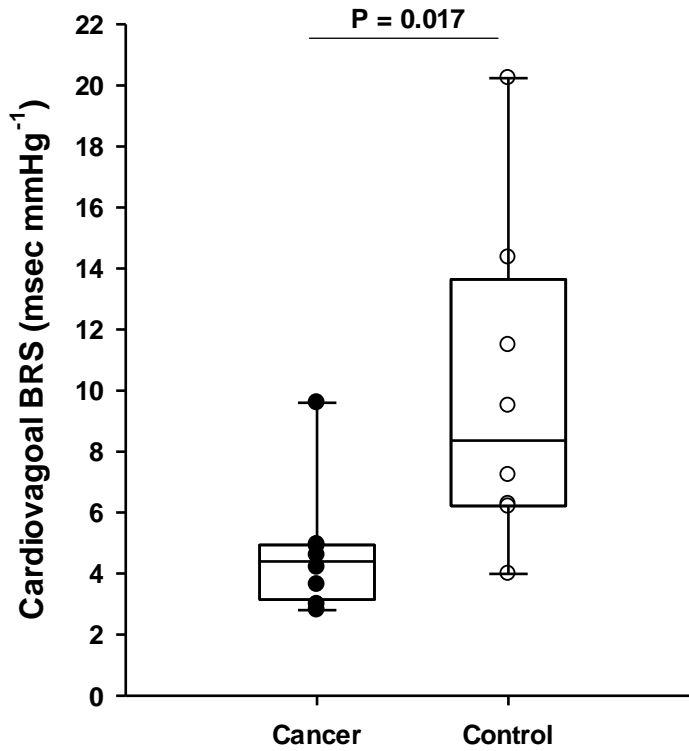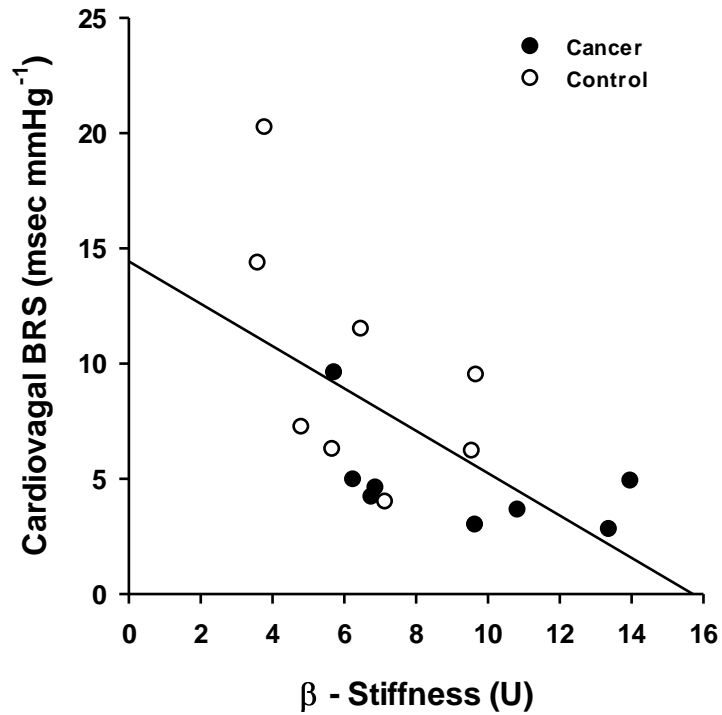
Figure 3 – **Linear regression between cardiovagal baroreflex sensitivity (BRS) and carotid artery β-stiffness.** The linear regression analysis revealed a significant relationship between carotid artery stiffness and cardiovageal baroreflex sensitivity (BRS) with a P = 0.007, indicating that sensitivity was decreased as stiffness increased.

Chapter 4 -   Discussion

The present study addressed the question of whether the use of chemotherapeutic treatment in cancer patients resulted in arterial stiffening and changes in arterial blood pressure control in cancer patients compared to healthy controls. Previous investigators have identified that within months of finishing chemotherapeutic treatment patients demonstrate evidence of cardiac and arterial damage (11, 26, 41). Our work expands on these findings and revealed that anti-cancer chemotherapy can have several detrimental effects on cardiovascular health within weeks of starting treatment. One such effect seen was an increase in carotid artery stiffness, which would decrease the ability of the arteries to distend when faced with increases in flow. This increased stiffness was quantified via calculation of both a β-stiffness coefficient and cross-sectional arterial compliance. In addition, decreases in spontaneous cardiovagal BRS was decreased in our group of chemotherapy treated cancer patients and modestly associated with the observed decreased compliance. These findings support our hypothesis that A) arterial stiffness would be increased in chemotherapy patients compared to healthy controls and B) the BRS would be decreased in chemotherapy patients compared to healthy controls.

Increased arterial stiffening is concerning because of the connection between increased stiffness and risk of cardiovascular disease (48). Even in otherwise healthy functioning older adults, increased arterial stiffness is predictive of future cardiovascular related mortality, chronic heart failure, and stroke occurrences (43). Arterial stiffening will naturally occur with age, and ultimately can be best avoided with exercise (44). Our data suggests that independent of age, treatment with chemotherapy significantly increases arterial stiffness, suggesting an overall worsening of the cardiovascular disease risk profile.

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Similar to our work, Mizia Stec et al. (41) demonstrated an increased arterial stiffness following adjuvant chemotherapy in breast cancer patients, while Chaosuwannakit et al. (11) showed similar results in breast, lymphoma, and leukemia patients receiving chemotherapy. Additionally, Jenei et al. (26) has shown increased arterial stiffening in childhood cancer survivors. Our data support these previous findings, showing increases in arterial stiffness in our group of chemotherapy patients compared to healthy controls.

The development and progression of arterial stiffness is a multifactorial process that involves the interaction between structural and cellular elements of the vessel wall, specifically the tunica adventitia, vascular smooth muscle, and the endothelium. The tunica adventitia consists of collagen fibers for structural integrity and elastin for distensability. A proper ratio of these two is required for the arteries to properly function. In both normal aging (30, 46, 52) and with cardiovascular disease progression (48) we see increases in arterial stiffness as well as an increase in the collagen:elastin ratio. Over time and with increased wall stress, degradation of elastin can occur (52) as well as increases in collagen content (56). This decay in elastin can occur due to calcium binding to the elastin fibers (60) and dysregulation of elastases (52, 64, 61). Direct binding of calcium ions to elastin causes calcification and decreases the elastic properties of the elastin. Increased activity of matrix elastases with age (64) results in more elastin fibers being degraded, which has been shown to accompany an increase in collagen:elastin ratio and decrease in functionality (29, 59, 19). Lastly, age related changes in amino acid profile decrease the availability of the amino acids desmosine and isodesmosine (63), which are required for proper crosslinking of elastin fibers, and with their decreases in availability result in a decrease in the elastic properties of elastin. While elastin is severely inhibited by disease and age, collagen concentrations increase. This can occur as a result of phenotype changes at the level of the

smooth muscle resulting in an increase in collagen formation across multiple layers of the artery (28), as well as through increased glycation of collagen fibers (53, 56).

The vascular smooth muscle is responsible for maintaining tone in the arteries and can be adversely altered in a variety of ways. Phenotypic changes of the smooth muscle can occur after prolonged periods of stress (28). This phenotypic change is often accompanied by cellular trans-differentiation, which is considered the main driving factor for increases in arterial calcification (28). This is because it changes the smooth muscle into a mediator of bone formation, causing increased calcification throughout the artery (28). Cellular trans-differentiation appears to be induced by a variety of factors that can be detrimental to the vasculature, namely; elastin degradation, increased reactive oxygen species, and fibrosis (28).

Endothelial changes in the arteries affect signaling pathways that cause some of the changes examined in the tunica adventicia and smooth muscle. The endothelium is an important site for the nitric oxide (NO) signaling pathways, whose effects are wide in scope. Decreased NO bioavailability is present with chronic inflammation (28), increase reactive oxygen species (28) and is considered associated with mechanisms that contribute to arterial stiffening (31). These increases in reactive oxygen species could then be a driving force for the cellular trans-differentiation occurring the smooth muscle. Additionally, chronic inflammation has been shown to decrease the production of psrostacyclin, which usually assists in vasodilation and inhibits platelet aggregation (42, 13).

There are a variety of possible mechanisms for this increased arterial stiffness with chemotherapy. First, increased inflammation resulting from the therapy could be impacting arterial stiffness in a similar way to what's been seen in other chronically inflamed populations (3, 46). Second, peripheral neuropathy has been identified as a possible side effect to a variety of

chemotherapeutic drugs, which could be detrimental to BRS (39, 40). Lastly, oxidative stress could be a mechanism as current evidence suggests that antioxidant supplementation can dampen these responses in certain models (6, 15). As seen in Table 1, a variety of chemotherapeutic drugs were used by our patient population and many of these drugs are associated with cardiovascular complications. Anthracyclines are associated with both acute and chronic progressive cardiomyopathy as well as increases in reactive oxygen species (15, 61), and were used by four of our patients. Two of our patients were treated with antimetabolites, which have been associated with increased risk of angina pectoris, myocardial infarctions, hypotension, and arrhythmia (17, 34, 49). Antimicrotubule agents were used on five subjects and have been associated with hypotension, arrhythmia, and neuropathy (4, 51). Monoclonal antibodies have been associated with hyper/hypotension, angioedema, and arrhythmias (20). These drugs were administered to three of our patients. Increased risk of chronic heart failure, neuropathy, and myocarditis have been associated with use of alkylating agents (18, 21), which five patient were administered. While there certainly is variety in the types of chemotherapy drugs administered to our patients, all drugs clearly have shown some sort of side effect that is detrimental to arterial function and potentially arterial stiffness.

Along with increases in arterial stiffness, we observed a significant decrease in cardiovagal BRS. Additionally, we observed a significant relationship between BRS and carotid artery stiffness. This supports previous work that observed a similar relationship in non-cancer popluations (43, 44). Baroreflex control of arterial blood pressure is achieved via a tonically active feedback loop. In a healthy individual, the arterial baroreflex will respond to increase in blood pressure by inhibiting sympathetic outflow. When stimulated, these baroreceptors increase afferent nerve firing rate, leading to increased stimulus of the nucleus tractus solitarius. This

subsequently leads to increased excitatory signals towards the caudal ventrolateral medulla and consequently increased inhibitory signals to the rostral ventrolateral medulla. This decrease in signaling to the rostral ventrolateral medulla causes a decrease in sympathetic outflow. Combining the effects of this, as well as the increased parasympathetic outflow courtesy of the nucleus ambiguus, results in decreases in heart rate, and vascular resistance, consequently leading to a decrease in blood pressure.

Given the integrated neural control of the arterial baroreflex, it is important to consider that many anti-cancer chemotherapies are associated with the development of neuropathy (20, 39, 40, 45, 55). We believe this, in combination with increased carotid artery stiffness, to be a likely factor in the decreased BRS observed in the cancer treatment group. To date there is a paucity of information regarding the effects of anti-cancer treatment on autonomic control of blood pressure, with limited evidence of clinical symptoms of autonomic dysfunction (i.e., arrhythmia, orthostatic hypotension). However, taxol chemotherapy (paclitaxel and docetaxel) are a subclass of chemotherapy drug that was used in five patients and has been shown to directly damage Schwann cells and axons of afferent neurons (4, 51). Additionally, Vinca rosea alkaloids in particular have been associated with neurotoxicity and/peripheral neuropathy (45), with one patient from the present study administered this class of drug. Additionally, the pro-inflammatory, antioxidant sparse condition brought on by chemotherapy treatments (6, 15) may have exacerbate the typical stimuli required to elicit detrimental effects on BRS. Decreased BRS is prevalent in a variety of disease states, including; hypertension, rheumatoid arthritis, and peripheral artery disease (3, 35, 41). All of these diseases share two common factors; a pro-inflammatory state, and an increase in arterial stiffness (3, 35, 41). While our evidence only can

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support the increased stiffness, we know that anthracyclines cause high levels of inflammation when administered (11, 26, 41).

Considerations and Limitations

There are numerous considerations to make when examining these data. First, our cancer population was quite varied, consisting of several types of cancer across just 8 participants. Additionally, these patients had very little crossover as far as specific drugs used in therapy plans. While this combination provided far less control in terms of identifying whether or not a specific drug was responsible for these circulatory problems, it does allow us to identify that these issues occur through chemotherapy in general. The second consideration to make is sample size. Lastly, this study was, by design, cross-sectional instead of longitudinal. We acknowledge it would have been preferential to test cancer patients before and after their treatment started, but given that our laboratory does not function inside and along an oncology office it is quite difficult to find participants in such a narrow window. For these patients and their doctors, starting treatment in a timely manner is a top priority. Because of that we designed the study in such a way to allow us to examine the effects of chemotherapy during its application. We believe this set our data apart by showing that these detrimental effects do not take months/years to develop, but rather occur early in the treatment process.

Conclusions

This is the first study, to our knowledge, to report the impact of adjuvant anti-cancer chemotherapy on changes in artery stiffness and baroreflex control of arterial blood pressure.

The findings of the present study suggest that chemotherapeutic cancer therapies are detrimental to arterial stiffness and BRS. While the specific mechanism cannot be determined with our data, and are only speculative at this point, the combination of our findings with previous studies suggest that several factors may be contributing to these changes: including the existence of a pro-inflammatory state, increases in reactive oxygen species, and the progression of chemotherapy-induced peripheral neuropathy. Future work will need to evaluate the role each of these factors has in mediating the adverse changes in cardiovascular health in cancer patients undergoing chemotherapy.

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