Impact of Cancer and Chemotherapy on Autonomic Nervous System Function and Cardiovascular Reactivity in Young Adults with Cancer: A Feasibility Study

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This is to certify that the thesis prepared

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complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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ABSTRACT

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Scott Adams

Despite therapeutic advances, cancer patients demonstrate an increased risk of developing disease- and treatment-related cardiovascular (CV) and metabolic morbidity, as compared to their peers. In light of emerging evidence, cancer- and treatment-related damage to the autonomic nervous system (ANS) may play a role in the development of the aforementioned morbidity risks. This assertion needs to be verified. The purpose of this study was to assess the feasibility of conducting concurrent ANS and CV evaluations in adolescent and young adult (AYA) cancer patients undergoing treatment for various cancers by defining the i) methodological pitfalls and best-practice criteria for ANS testing in cancer, and ii) provide initial physiologic evidence of autonomic perturbations in cancer patients using the composite autonomic scoring scale (CASS). Thirteen patients were assessed, pre-treatment (T1) and following 4 cycles of chemotherapy (T2), using CASS and a modified Astrand-Rhyming cycle ergometer protocol, and their results compared to 13 sex and age-match controls. Overall, the average success rate in achieving the targeted feasibility criteria (FC) was 98.5%. Additionally, according to the CASS, there was evidence of ANS impairment at T1 in 5 of 13 patients, which persisted in 4 of 12 patients at T2, compared to 0 of 13 controls at T1 and 1 of 12 controls at T2. Using a 2 x 2 repeated measures ANOVA, treatment led to a significant improvement in patient heart rate (HR) recovery [$F=6.188$, $p=0.027$]. Results from this feasibility study suggest the investigation of ANS function in AYA cancer patients undergoing chemotherapy is possible, provided the proper precautions are

taken. Furthermore, to the best of our knowledge, this is the first study to report evidence of ANS impairment using CASS and sudomotor dysfunction in this population.

Keywords: Cancer, autonomic nervous system, composite autonomic scoring scale (CASS), young adults.

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To my parents, thank you for always believing and never giving up. Words cannot describe how much you mean to me.

To my fiancée and my rock, Rhiannon. Thank you for your patience and encouragement. I could not ask for a better friend or partner. I cannot say life will be any less hectic as I enter into my PhD, but at least we will be together. I love you.

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List of Abbreviations

ADL - Activities of Daily Living
AE - Adverse Events
ANS - Autonomic Nervous System
AV - Atrioventricular
AYA - Adolescent and Young Adult
BFI - Brief Fatigue Inventory
BMI - Body Mass Index
BP - Blood Pressure
bpm - Beats Per Minute
CAN - Central Autonomic Network
CASS - Composite Autonomic Scoring Scale
CO - Cardiac Output
CV - Cardiovascular
CVD - Cardiovascular Disease
CVRC - Cardiovascular Reserve Capacity
DOX - Doxorubicin
Dx - Diagnosis
FC - Feasibility Criteria
HF - High Frequency
HR - Heart Rate
HRV - Heart Rate Variability
JGH - Jewish General Hospital
LF - Low Frequency
ME - Maximal Exercise
MSRC - Musculoskeletal Reserve Capacity
NR - Not Reported
NS - Nervous System
O_2 - Oxygen
OEP - Otherwise Eligible Patients
PA - Physical Activity – PA
PCM – Potentially Confounding Medication
PNS - Parasympathetic Nervous System – PNS
Pt – Patients
QSART - Quantitative Sudomotor Axon Reflex Test
RPE - Rate of Perceived Exertion
RSA - Respiratory Sinus Arrhythmia
SA - Sino-atrial
SD - Standard Deviation
SME - Sub-Maximal Exercise
SNS - Sympathetic Nervous System
T1 - Pre-Treatment or Baseline
T2 - Follow-Up
VM - Valsalva Maneuver
VO_{2max} - Maximal O_2 Uptake
VO_2 - O_2 Uptake

Author Contributions for the Manuscript

Scott Adams is the primary author of the manuscript included in this thesis and is responsible for subject recruitment, data collection and data analysis. He is also responsible for the writing of the thesis chapters preceding the manuscript.

Robert Kilgour is the main thesis supervisor to the primary author and oversaw the development of the project and the manuscript. Dr. Kilgour assisted in editing the entire thesis and manuscript.

Ronald Schondorf is the co-supervisor and laboratory supervisor to the primary author. Dr. Schondorf made a significant contribution to the theoretical, data collection and data analysis components of the thesis. Furthermore, Dr. Schondorf provided critically important intellectual content to the interpretation of the results and is the primary editor of the manuscript ensuring its accurateness and completeness.

Julie Benoit is responsible for supervising and assisting in data collection, data cleaning and primary analysis. She was also responsible for ensuring patient safety during all subjects' testing.

Chapter I

Cancer Survivorship: The Context of Late Effects

Engaging in regular exercise has been shown to enhance the function of almost every human system, including, but not limited to, the CV, musculoskeletal, endocrine, nervous, reproductive and gastrointestinal systems. Since the first studies were published in the mid-1980's, engaging in regular exercise has been shown to improve cancer prevention, management and recovery outcomes. Given cancer's heterogeneity, elucidating mechanisms by which exercise may benefit cancer patients continues to prove elusive. Unraveling the overlapping influences of patients' environment, genetics, behavior, lifestyle, pre-existing and age-related comorbidities from their specific cancer diagnoses and the multitude of surgical, local and systemic anti-cancer therapies is difficult. Nonetheless, many researchers are working to advance our understanding of key cancer-exercise risk factors, mechanisms of dysfunction and therapeutic benefits.

Recent reviews of the long-term impact of common cancer therapies from the 1970's to the 1990's have provided important epidemiological information regarding the late effects of treatment. These cancer survivors have a significantly increased risk of CV, metabolic, cognitive and functional impairments (**Section 1.1.2**). Improved diagnostic and screening techniques, surgical advances and new treatments (**Section 1.1 & 1.5**) have dramatically improved survival rates but the late-effects of treatment, combined with natural age-related comorbidities, may pose serious risks for these survivors. As such, greater emphasis should be placed on developing and improving follow-up and related comorbidity prevention strategies.

Some of these strategies can be inferred from the related risk factors that exist for developing CV/metabolic diseases and cancer, as well as for developing CV and

metabolic sequelae years after the cessation of cancer therapy (Demark-Wahnefried, Aziz, Rowland, & Pinto, 2005). These common risk factors do not establish a true cause and effect relationship between developing cancer and CV and metabolic morbidity. Nonetheless, it would stand to reason that any strategy known to improve CV function should at least be considered in patients with cancer.

One possible common link may be the effect of cancer its therapy on ANS function. A relationship between indices of autonomic function and the incidence and severity of CV morbidity is well supported in the literature. Whether poor autonomic function causes, or simply predicts CV morbidity has not been well defined. If a causal relationship exists, the preservation and restoration of autonomic function may prevent the development of CV and metabolic comorbidities (**Section 1.4**). Alternatively, the assessment of autonomic function in cancer patients and survivors may provide important prognostic information regarding future CV morbidity. Thus far, the evaluation and reporting of cancer-related ANS impairment has been inconsistent (**Section 1.5**) and has been hampered by the wide age range of patients studied. Since ANS function naturally declines with age, investigations using a younger population should better highlight any influence of cancer and anticancer therapies on ANS function.

We have extensive experience with these younger patients who are treated within the McGill AYA Oncology Program. We know that despite the presence of recurrent and advanced disease (42% of study participants), these patients remain highly motivated and compliant with exercise prescriptions (Dalzell et al., 2010). These factors, coupled with the general lack of age related comorbidity make them a physiologically ideal cohort to begin assessing incidence and mechanisms of cancer-related ANS dysfunction.

1. Introduction

1.1.1 Burden of Adolescent and Young Adult Cancer in Canada

In general, AYAs face a unique subset of life stage-related issues and challenges to self-identity, relationships, fertility, personal and financial independence (Zebrack et al., 2013). A cancer diagnosis (Dx) makes these issues even more burdensome and difficult to confront. In recent years, evidence has emerged highlighting multiple healthcare- and support-disparities between the AYA cancer age group and their younger and older oncology counterparts (Bleyer, 2007). One hundred thousand new AYA cancer diagnoses (aged 20-44 years) were reported in Canada between 1990 and 1999 (Ontario, 2006). Although it is true that 5-year survival rates (**Figure 1**) (72% survival men & 81% women (Ontario, 2006)) in this group have been quite high, these rates have not changed since the mid 1970's (**Figure 2**). In contrast, survival rates of younger and older patient groups have improved. The reasons for this distinction are unclear. Perhaps the tumour biology and physiology is different (Bleyer et al., 2008), or perhaps these patients have fallen between the cracks in the healthcare system as evidenced by the late diagnosis of their cancer **(Section 1.1.2)**, poor tracking and enrolment in AYA clinical trials, treatment centres and support programs (Bleyer, 2007).

1.1.2 Late Effects of Cancer and Related Treatment

As noted above, diagnosis of cancer in the AYA group is often delayed (Bleyer, 2002, 2007). As a result of these delays cancers are often more advanced at diagnosis and more aggressive treatment strategies are often required. These treatments often cause neurocognitive dysfunction, fertility and gonadal dysfunction,

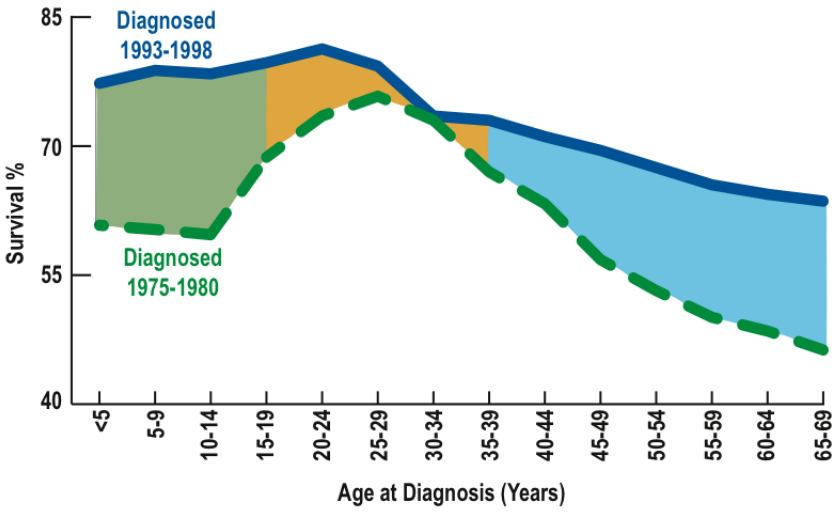


Figure 1: 5-Year Survival of Patients with Cancer by Era, SEER, 1975-1998
(National Institutes of Health, 2006)

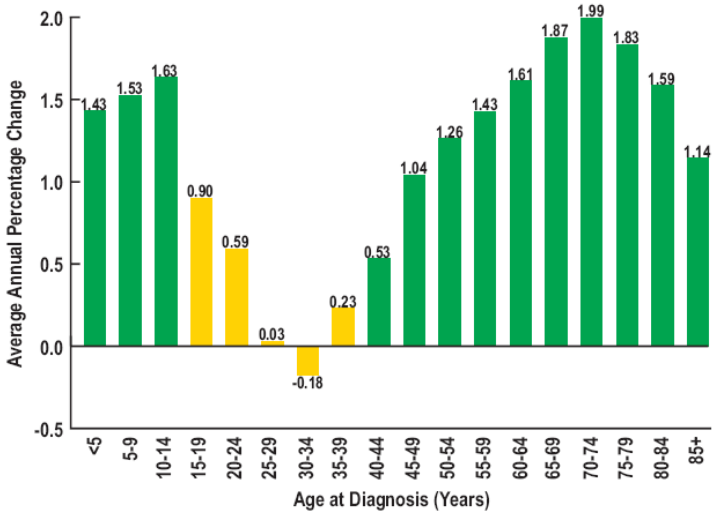


Figure 2: Improvement in 5-Year Relative Survival, Invasive Cancer, SEER, 1975-1997
(National Institutes of Health, 2006)

serious psychosocial issues, heart disease, stroke, diabetes, hypertension, dyslipidemia, obesity, renal insufficiency, subsequent malignancies, and decreased muscle mass (Demark-Wahnefried et al., 2005; Oeffinger, Nathan, & Kremer, 2010). Studies of pediatric cancer survivorship have highlighted the following alarming trends: i) approximately ¾ of survivors will develop a chronic disease by age forty, with >40% of

those diseases being serious (Geenen et al., 2007; Oeffinger et al., 2006), ii) even 30 years or more after post Dx, there is a significantly increased risk of premature death (from a second cancer or cardiopulmonary disease) (Mertens et al., 2001; Moller et al., 2001) and iii) approximately 50% of long term survivors will experience diminished health status (moderate to severe) (Hudson et al., 2003; Ness et al., 2005).

1.1.3 Societal Burden of AYA Cancer

As a result of persistent disease and treatment-related damage, AYA cancer survivors may be at risk of long-term complications impacting their health, quality of life (QOL), functional independence, and may seriously hinder their ability to reintegrate and meaningfully contribute to society. Combining incidence, 5-year survival, and mortality data (Canada, 2012; Ontario, 2006) with average life expectancy (Canada, 2012), crude calculations approximate that, every year, the lingering effects of new Canadian AYA cancer diagnoses have the potential to impact over 350,000 years of productive adult life (see **Appendix A** for calculation summary). This represents a tremendous burden to society. Furthermore, it underscores the importance of developing and implementing prevention strategies targeting these late effects. However, before targeted strategies can be developed, we must better understand the specific mechanisms of disease- and treatment-related damage.

1.2 Autonomic Nervous System

1.2.1 Basic Structure and Function

The ANS exerts control over visceral functions at multiple levels. The central autonomic network (CAN) is comprised of multiple, reciprocally interconnected areas

within the hypothalamus, brain stem and spinal cord. The CAN serves as the reception and integration center for afferent visceral, humoral and environmental stimuli and elicits coordinated reflex responses via efferent preganglionic autonomic, neuroendocrine, respiratory and sphincter motoneurons. These tonic and adaptive reflex responses are relayed to effector organs via the parasympathetic and sympathetic ANS branches and are influenced by a variety of internal and external environmental states and stimuli (e.g. circadian, postural, acute exercise or emotional factors) (Benarroch, 1997; Guyton & Hall, 2006a).

The parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) are distinctly different in both structure and function. Structurally, the functional unit of the PNS is comprised of long, myelinated preganglionic efferent fibers that synapse with short unmyelinated postganglionic neurons. These PNS relay ganglia are typically found in close proximity to or within the individual organs they innervate. Conversely, the SNS is comprised of shorter myelinated preganglionic neurons that synapse with longer unmyelinated postganglionic neurons. Unlike the PNS relay ganglia, the divergent efferent fibers leading away from the SNS relay ganglia innervate multiple effector organs and organ regions. According to these structural differences, damage to SNS relay ganglia or postganglionic fibers may manifest as multi-organ or systemic failure, whereas typical presentation of postganglionic PNS damage is more localized (Guyton & Hall, 2006a; Harati & Machkhas, 1997).

1.2.2 Autonomic-Cardiovascular Control

The CV system is comprised of the heart, lungs, peripheral vasculature and blood. As a functional unit, the CV system continuously adjusts to maintain organ blood flow and peripheral oxygen (O_2) delivery via regulation of cardiac output (CO) and

systemic vascular resistance. This dynamic and finely tuned CV control is achieved through the synergistic action of both PNS and SNS branches on key effector organs (e.g. heart and lungs), as well as CAN-mediated neuroendocrine effects and local factors (Joyner & Shephard, 1997).

Various local and neural mechanisms influence CO, including venous return (the Frank-Starling mechanism), local and peripheral tissue metabolic demands, systemic vascular resistance and respiration rate (Guyton & Hall, 2006b). HR is intrinsically driven by both an intrinsic cardiac nervous network (similar to the enteric nervous system (NS) of the gut (Randall et al., 2003)) and the periodic, spontaneous depolarizations of the sino-atrial (SA) node (Yasuma & Hayano, 2004). The SA node, the atrioventricular (AV) node, and the atrial and ventricular (SNS only) myocardium, are dually innervated and modulated by the PNS and SNS. In general regulatory or homeostatic terms, stimulation from the SNS increases CO by increasing ventricular contractility or the rate of cardiac depolarization (Berntson, Cacioppo, & Quigley, 1993; Yasuma & Hayano, 2004). Conversely, stimulation from the PNS acts in a reciprocal manner to effectively decrease HR, cardiac muscle conduction, atrial contractility and ventricular contractility via the counteraction, and reflex-dependant inhibition, of the SNS (Randall et al., 2003; Yasuma & Hayano, 2004). Beyond the classic 'opposite and reciprocal' ANS branch function characterization, multiple animal studies have demonstrated that specific and perhaps protective autonomic reflex responses to peripheral chemoreceptor, startle, pain and ocular trauma stimuli elicit co-activation of the autonomic branches (Patton, Vogel, & Mello, 1982). These co-activation states have been shown to elicit biphasic (i.e. startle (Abdeen, Taylor, Youngblood, & Printz, 1995; Baudrie, Tulen, Blanc, & Elghozi, 1997; Casto, Nguyen, & Printz, 1989; Casto & Printz, 1990; Haroutunian & Campbell, 1982)), tachycardic (i.e. somatic nociceptors (Abram, Kostreva, Hopp, & Kampine, 1983;

Adams, Baccelli, Mancia, & Zanchetti, 1969; Barr, 1998; Boscan & Paton, 2001; Martin, Sutherland, & Zbrozyna, 1976)) and bradycardic (i.e. peripheral chemoreceptor (Kollai & Koizumi, 1979)) HR responses. Also under ANS control, HR is further affected by local and peripheral reflex responses and by fluctuations in respiration rate (Berntson et al., 1993; Yasuma & Hayano, 2004). These dynamic and synergistic mechanisms of control are necessary to quickly and efficiently adapt the heart's chronotropic, inotropic and dromotropic parameters to the body's dynamic metabolic needs and various environmental stimuli. Importantly, the reciprocal activation and coactivation patterns of ANS control play important complementary roles. Reciprocal activation is known to evoke rapid reflex adjustments whereas coactivated responses permit greater response precision.

Our understanding CV reserve capacity (RC) began with mechanisms identified in the heart (Frank, 1895; Starling & Visscher, 1927). We now know this CVRC, inclusive of multiple CV system components, protects our functional capacity against varying degrees of pathological insult by way of coordinated adaptation (Hsia, 2001). However, the adaptive potential of our CV system is not limitless. As such, repeated pathologic injury to any (or multiple) system component(s) or chronic pathologic perturbations may eventually result in dysfunction. In humans, initial evidence of impairment to either ANS branch typically presents within the effector organ(s) they innervate (Ziegler, 1999). Two of the many systems affected by autonomic neuropathies are the CV (or O_2 transport system) and the sudomotor system (Vinik, Maser, Mitchell, & Freeman, 2003). If damaged, the resulting decrease in muscle O_2 availability and metabolic waste product clearance or thermoregulatory impairment could negatively impact functional performance, independence and quality of life. Although ANS dysfunction is known to

affect systems other than the CV and sudomotor systems, their relative ease of measurement provides a safe and tolerable means of autonomic assessment.

1.2.3 Clinical Laboratory Assessment of Autonomic Function

The assessment of autonomic function in humans is complex because autonomic control, like most control systems, is a closed loop and hence individual components such as heart rate or blood pressure do not exist in isolation. Furthermore, due to the invasiveness of the procedures required, the direct measurement of ANS activity in conscious humans is either difficult or impossible. Accordingly, human investigations of ANS function rely on indirect assessment techniques and are therefore subject to additional sources error. Although a variety of laboratory and clinical autonomic challenges and interpretation techniques have been developed, none are without limitations (several of which are described briefly here).

Clinical investigations of human autonomic function impose simple, non-invasive, physiologic challenges, such as the ones described below, in an attempt to elicit predictably patterned reflex responses. Despite the apparent simplicity of the imposed challenges, even the simplest reflex response is quite complex. Stimuli are registered by somatic sensory organs, relayed along afferent nerve fibers to the CAN for processing, are processed along with afferent information from other receptor groups, and are then transmitted along efferent nerves to the appropriate effector organs. Damage or dysfunction within any one of these structures may impact the resultant reflex response. Further complicating the issue, there are currently no available means of quantifying the inputs to the multiple receptor groups that mediate, these complex reflex responses. The underlying physiology is often incompletely understood and some use complex

mathematical models, which may not accurately characterize specific ANS branch activity.

Despite the multitude of potential confounders and our current inability to quantitate and control the physiologic strain imposed by clinical autonomic challenges, the presence or absence of predictable autonomic adjustments may still provide important prognostic and diagnostic information. Although an exhaustive discussion of ANS testing is beyond the scope of this review, a brief summary of the general characteristics of several clinical autonomic challenges is provided below.

1.2.3.1 Respiratory Sinus Arrhythmia

Respiration (both depth and frequency of breathing) strongly modulates HR rhythmicity generating a rhythm known as respiratory sinus arrhythmia (RSA) (**Figure 3**) (Berntson et al., 1993). This phenomenon results from, and is modulated by, the complex interaction of factors originating in the heart (the Bainbridge stretch reflex), lungs (the Hering-Breuer stretch reflex), CAN (inspiration-associated inhibition of vagal efferents within the medullary respiratory center) and vasculature (respiration-associated tonic and phasic baroreceptor and chemoreceptor modulations), as well as local mechanical and metabolic factors (Davies & Neilson, 1967a, 1967b; Feldman & Ellenberger, 1988; Grossman, 1983; Guyton & Hall, 2006a; McArdle, Katch, & Katch, 2007; Saul, Rea, Eckberg, Berger, & Cohen, 1990).

RSA naturally occurs across a range of respiratory frequencies but is most commonly assessed through the analysis of the frequency and amplitude of HR variability (V) during controlled deep breathing. This indirect index of cardiovagal function has been suggested to be specific, sensitive and reproducible (Freeman, 1997).

Described in dogs (Katona & Jih, 1975), and later in humans (Fouad, Tarazi, Ferrario, Fighaly, & Alicandri, 1984), parasympathetic cardiac control is characterized as the decrease in HR period resulting from eliminated parasympathetic influence (with preserved sympathetic influence). RSA is defined as the peak-to-trough difference in RR interval in a series of respiratory cycles (Freeman, 1997). RSA is typically performed with the patient supine, where, due to a decrease in baroreceptor-mediated sympathetic activity, vagal influence is greatest. The greatest amplitude of RSA-mediated HR response is achieved with maximal respiratory effort and at a respiratory rate of four cycles per minute.

Although a range of respiratory cycles have been used, RSA is most commonly assessed using a comfortably slow respiration rate of six cycles per minute and the average peak-to-trough difference from the largest six sequential responses (Freeman, 1997). Through a range of respiratory frequencies, the R-R interval is shortened when the cardiac vagal nerve activity is nearly arrested during inspiration and lengthened during expiration when cardiac vagal nerve activity reaches its peak (**Figure 3**). Although some groups have generally consider RSA as a reliable, clinical index of cardiac vagal activity (European Society of Cardiology & North American Society of Pacing Electrophysiology, 1996; Yasuma & Hayano, 2004), several other factors have been shown to modify this reflex response (i.e. state-dependant sympathetic influences, circulating catecholamine levels, central and peripheral chemoreceptor stimuli and respiratory-linked mechanical factors (i.e. atrial stretch) (Taylor, Myers, Halliwill, Seidel, & Eckberg, 2001; Yasuma & Hayano, 2004).

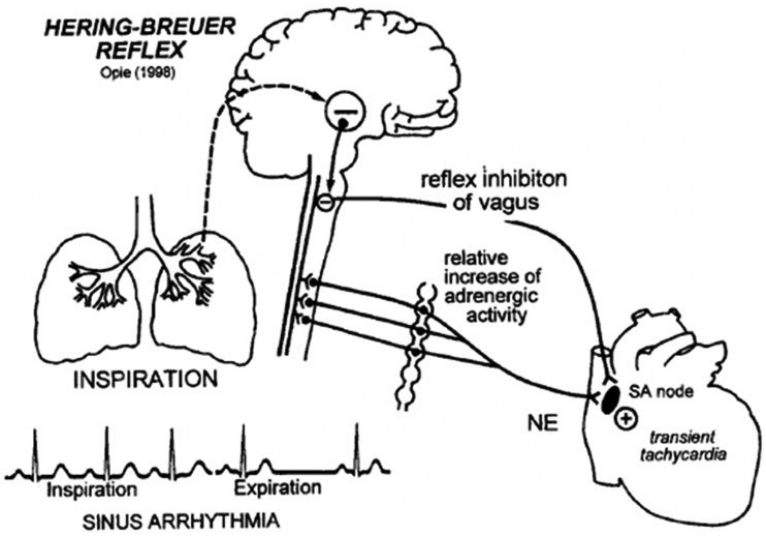


Figure 3: Basic RSA physiology
(Verrier & Tan, 2009)

Clinically, the magnitude of R-R difference during inspiration and expiration indicates the amplitude of RSA (Eckberg, 1983; Katona & Jih, 1975). This amplitude is quantified through high frequency (HF) component spectral analysis of electrocardiographic recordings in the range of (0.15 Hz – 0.80 Hz) (Yasuma & Hayano, 2004). Age related trends show the amplitude of RSA is greatest in younger populations and is attenuated with age (Hrushesky, Fader, Schmitt, & Gilbertsen, 1984). Within a given age group, well-trained individuals have greater RSA amplitude than their untrained counterparts (Dixon, Kamath, McCartney, & Fallen, 1992; Goldsmith, Bigger, Steinman, & Fleiss, 1992a). Reduction of RSA (**Figure: 4**) has been reported in patients with coronary artery disease or congestive heart failure (Airaksinen, Ikaheimo, Linnaluoto, Niemela, & Takkunen, 1987; Hayano et al., 1990; Myers et al., 1986) and is suggested to be one of the most easily quantified markers of autonomic neuropathy in the diabetic population (Lishner et al., 1987).

Normal Response **Abnormal Response**

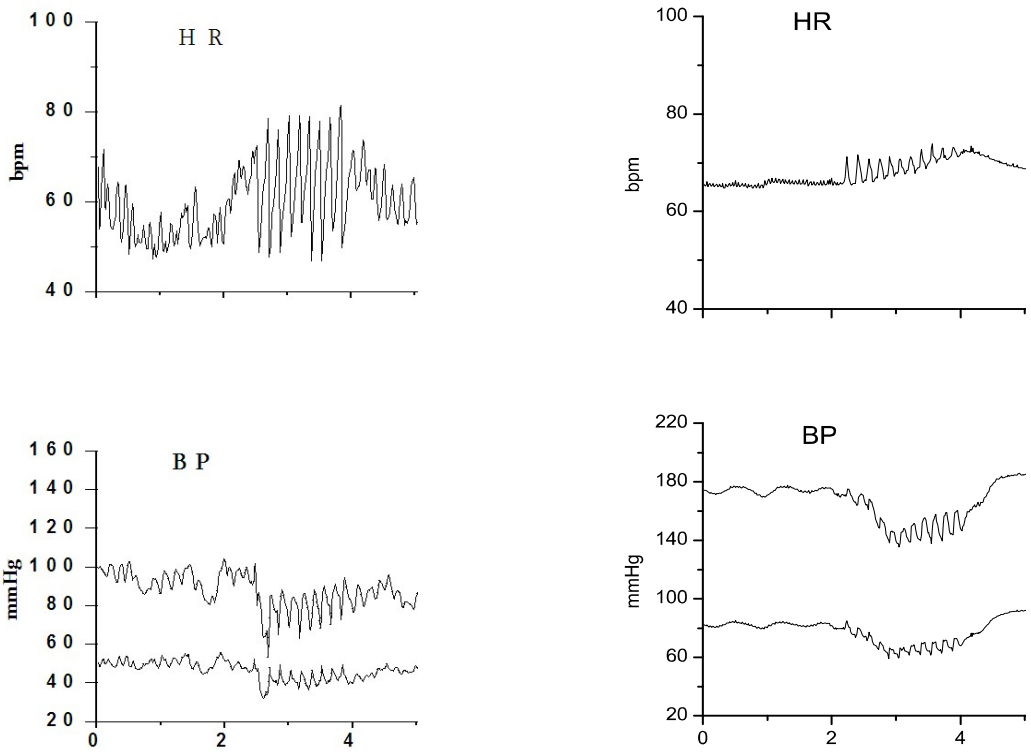


Figure 4: Normal and abnormal HR and BP responses to controlled deep breathing (6 breaths/min) (Clinical data – Schondorf, 2013)

1.2.3.2 Valsalva Manoeuvre

In his book published in 1704, physician Antonio Maria Valsalva first described a technique for clearing foreign bodies from the middle ear via a forced expiration against a closed glottis (Junqueira Jr., 2008). Now known as the Valsalva Maneuver (VM), this reflex response provides the physiological basis for our understanding of CV adaptations to forced expiration (Amorim, Manço, Gallo Jr, & Marin, 1982; Eckberg, 1980; Elisberg, 1963; Freeman, 1997; Junqueira Jr. & Soares, 2002). Despite the VM's apparent simplicity, the resultant reflex response to this challenge is quite complex. The physiologic response to the VM is divided into four simultaneous and serially alternating changes in HR and BP (as described in **Table 1)**.

Table 1: Mechanical and Hemodynamic Response to Valsalva

Maneuver Phases	Mechanical Factors	Hemodynamic Response
Phase I (inspiration)	• Aortic compression • Blood forced into peripheral circulation	↑ BP ↓ HR
Phase II (expiration)	• ↓ CO (poor venous return)	↓ BP (early phase) ↑ HR (cardioacceleration) ↑ Muscle sympathetic activity ↑ Peripheral resistance ↑ BP (late phase)
Phase III (relaxation)	• Cessation of expiration	↓ BP ↑ HR
Phase IV (relaxation)	• Residual vasoconstriction • Normal venous return	↑ BP above baseline (overshoot)* ↓ HR (baroreflex-mediated)

* primarily due to cardioacceleration
Content adapted from (Freeman, 1997)

Although a variety of variations have been reported, the basic VM is described as follows. After two minutes of supine rest, and following a full inspiration, the subject breathes into a tube and maintains an expiratory pressure of 40 mmHg for 15 seconds. The subject's beat-to-beat HR and BP responses are collected throughout and in recovery from the maneuver. After an additional two minutes rest, the subject is asked to perform a second trial (Junqueira Jr., 2008). The multiple, sequential and overlapping mechanisms contributing to a normal hemodynamic response to the VM are reasonably well understood. Importantly, given the VM's complexity, many factors have been shown to impact the response including (but not limited to) straining initiation, mouth pressure, expiratory duration, body position and post-maneuver breathing response. Furthermore, the presence and magnitude of the resultant, phase-specific HR and BP responses are interdependent. It is this reflex response interdependence which makes it considerably more difficult to unravel the mechanisms underlying aberrant responses (Eckberg, 1980).

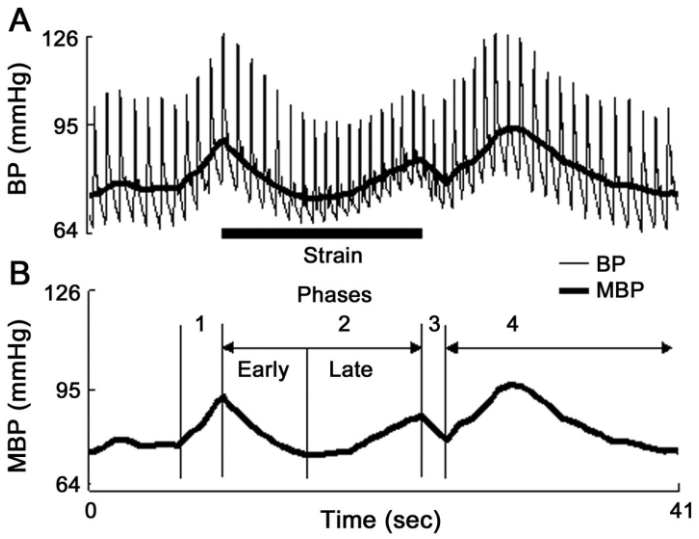


Figure 5: BP response to the VM
(P. Novak, 2011a)

With the understanding that mechanical factors are known to contribute throughout, several components of the VM response have been identified as being the most informative of ANS control (Eckberg, 1980). Early (Phase I) cardioacceleration likely reflects vagal withdrawal, whereas late (Phase IV) HR recovery is thought to be influenced by vagal reactivation. Similarly, late Phase II BP recovery is dependant on sympathetically-mediated peripheral vasoconstriction, which also influences the Phase IV BP overshoot. However, given their interdependence, the analysis or interpretation of any singular component of this reflex response is meaningless. Moreover, the VM is especially vulnerable to the previously described pitfalls of ANS testing requiring the results to be interpreted with caution. A more detailed description of how these components contribute to CASS is provided in **Section 1.2.3.6**.

Investigation of this maneuver through time-domain indices of HRV and BPV has been described as being a sensitive, reliable, reproducible and simple tool in approximating cardiac autonomic adjustments in a number of pathologies including:

diabetes mellitus (Baldwa & Ewing, 1977; Bennett, Farquhar, Hosking, & Hampton, 1978), various CV diseases (Rostagno et al., 2000; Trimarco et al., 1983; Tristani, Kamper, McDermott, Peters, & Smith, 1977), renal failure (Ewing & Winney, 1975) and neurological diseases (De Marinis, Stocchi, Gregori, & Accornero, 2000; Lyu et al., 2002).

Normal Response **Abnormal Response**

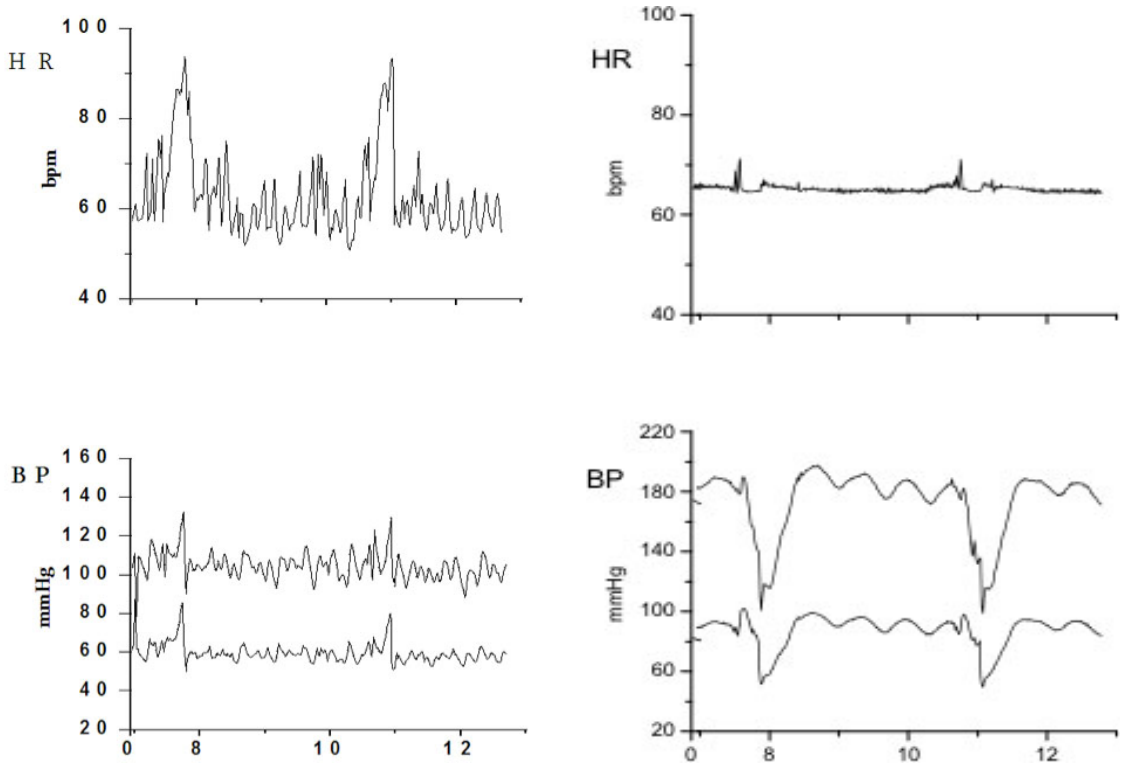


Figure 6: Normal and abnormal HR and BP responses to VM
(Clinical data – Schondorf, 2013)

1.2.3.3 Tilt-Table Test

Utilizing a postural change from supine to upright, a second challenge used to assess the integrity of baroreceptor function and its contribution to ANS reflex responses is called the tilt-table test. Compared to voluntary standing, the advantage of using the tilt-table challenge lies in the partial elimination the voluntary and exertion components,

and better control in the event of syncope (Borst, van Brederode, Wieling, van Montfrans, & Dunning, 1984; Borst et al., 1982). The assumption of upright posture causes a shift of 6-8 ml/kg of blood from the thorax into the abdomen and lower extremities (Joyner & Shephard, 1997; Smit, Halliwill, Low, & Wieling, 1999). The blood translocation begins immediately, with upwards of 50% of the shift occurring within seconds. The resulting reduction in central blood volume decreases cardiac filling pressure and ultimately a drop in stroke volume (≈ 40%) (Smit et al., 1999). Reflex tachycardia, likely caused by vagal withdrawal to the SA node and increased sympathetic activity, partially compensates for the drop in stroke volume and limits the fall in CO to ≈ 20%. This cardiac compensation, along with the sympathetically-mediated increase in systemic vascular resistance, is able to maintain mean arterial BP. Overall, the maintenance of the mean arterial pressure is dependant on a complex series of mechanisms including the venoarteriolar axon reflex, pulmonary stretch reflex, cardiopulmonary reflexes and arterial baroreflexes (Joyner & Shephard, 1997; Smit et al., 1999).

The primary circulatory differences associated with tilt, compared to supine circulation, are summarized in **Table 2**. Beat-to-beat BP and HR changes in response to head-up tilt are measured and compared against expected deviations from supine measures. Normally, subject BP and HR adaptation takes place within the first 1-2 minutes of tilt and remains stable until returned to a supine position (typically after 10 min) (Wieling & van Lieshout, 1997).

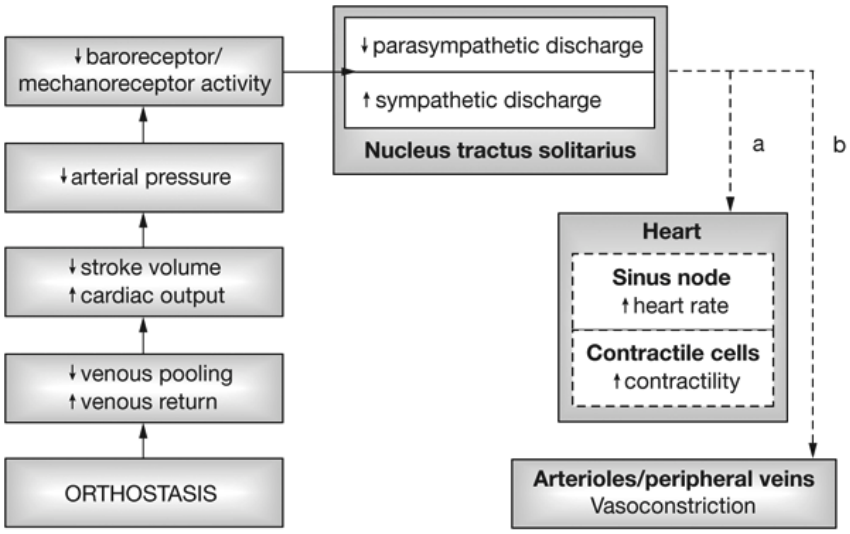


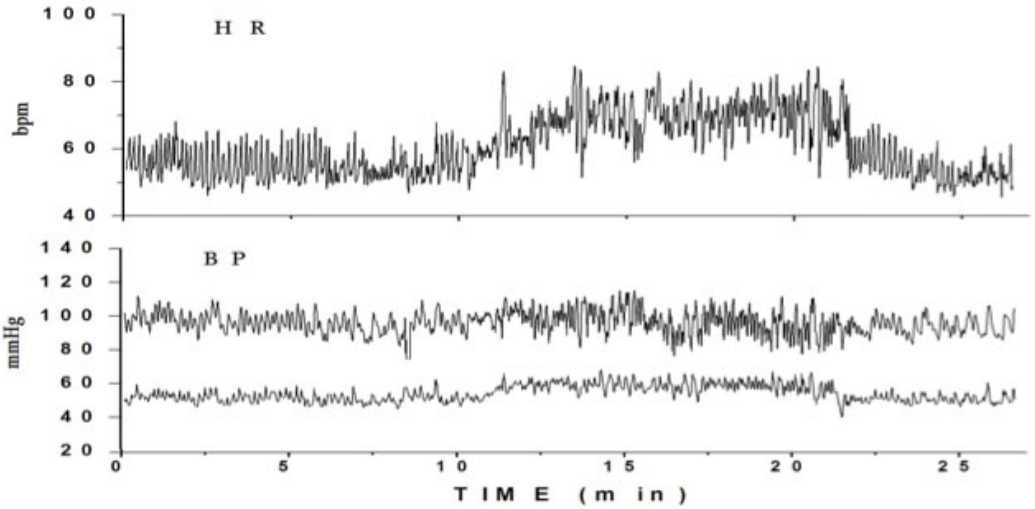
Figure 7: Pathway of orthostatic compensation
(Yusuf & Camm, 2005)

Table 2: Expected BP & HR Response to Head-Up Tilt

Hemodynamic Property	Expected Compensation
Intrathoracic Blood Volume	↓ 30%
Stroke Volume	↓ 30-40%
HR	↑15-30%
CO	↓ 20%
Arteriovenous O_2 Difference	↑ 20%
Diastolic BP	↑ 10%
Systolic BP	Unchanged
Mean Arterial Pressure	↑ 0-10%

Content adapted from (Wieling & van Lieshout, 1997)

Normal Response



Abnormal Response

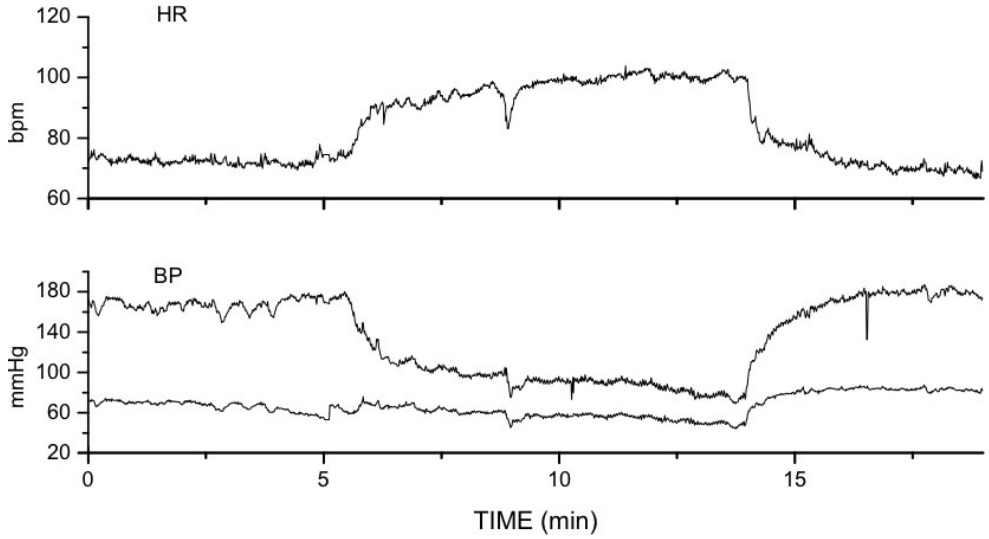


Figure 8: Normal and abnormal HR and BP responses to 80^{o} head-up tilt (Clinic data – Schondorf, 2013)

1.2.3.4 Heart Rate Variability: Overview and Applications

Physiologically, the fluctuation in R-R intervals (**Figure 9**) is the result of complex interactions between the PNS and SNS and of other non-neurally mediated influences, like hormones and intrinsic intracardiac pacemakers. Given that vagal nerve activity cannot be directly measured in humans, indirect measures of autonomic function, such

as HRV, have become widely used. Beginning with the discoveries of variable beat-to-beat heart periods (Hales, 1733; von Haller, 1760) and autonomic modulation in both the time (Wheeler & Watkins, 1973) and frequency (Sayers, 1973) domains, mathematics-based HRV analysis techniques have been employed for decades as a non-invasive means of approximating the nature of the ANS's control over the CV system and the dynamic nature in which they interact (European Society of Cardiology & North American Society of Pacing Electrophysiology, 1996).

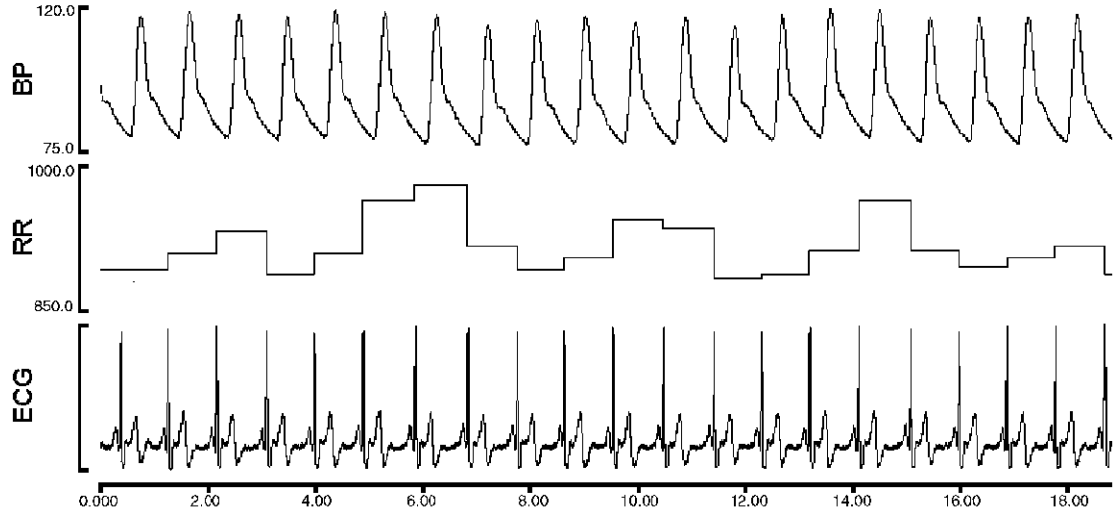


Figure 9: Arterial BP (top, mmHg), R-R Interval (middle, ms), and ECG (bottom) demonstrates variation of the inter-beat interval (de Jong & Randall, 2005)

HRV data is commonly collected under a variety of conditions and settings including rest (spontaneous and controlled breathing), in response to known ANS challenges (RSA, VM, Head-up Tilt, sustained hand grip, standing, and under emotional and mental stress) and over prolonged collection periods (24-Holter monitoring). Analysis of time and frequency-based oscillations in heart period require the use of increasingly complex mathematical techniques and, in doing so, has been able to approximate and make inferences around ANS activity in a host of healthy and disease-

based physiologic states (Rosenwinkel, Bloomfield, Arwady, & Goldsmith, 2001; Thayer & Lane, 2007). Standard time domain indices of HRV are described in **Table 3**. Commonly controlled confounders of HRV collection and analysis include, but are not limited to: i) unrecognized ectopic beats, ii) duration and state of collection, iii) respiratory frequency and depth, iv) age, v) circadian variation, vi) certain anthropometric indices (body weight & body mass index (BMI)), vii) blood gases, viii) physical fitness, ix) food ingestion and x) certain medications (especially anticholinergic). Even with adequate data collection controls in place, given its complexity and numerous confounders, great care must be taken when analyzing and interpreting HRV data.

Table 3: Time Domain Measures of HRV

Measure	Definition
SDNN	- Standard deviation (SD) of normal-to-normal (NN) RR intervals (24-hr recordings)
SDNN index	- Mean of SD of the RR intervals (5 min segments from 24-hr recordings) - Correlates with Very Low Frequency (VLF) (0.0033-0.04 Hz) & Low Frequency (LF) (0.04-0.15 Hz) HR power spectrum
SDANN index	- The SD of the mean RR intervals (5 min segments from 24-hr recordings) - Correlates with Ultra Low Frequency (ULF) (< 0.0033 Hz) HR power spectrum
MSSD	- The average of the square of the differences between successive HR beats
rMSSD	- Square root of MSSD (measure of short term HRV) - Correlates with High Frequency (HF) (> 0.15) HR power spectrum
SDSD	- Stand deviation of successive differences

Content adapted from (Freeman, 1997)

Frequency-domain analysis of HRV is another commonly used approach to quantify ANS activity (**Figure 10**). Parasympathetic efferent output has been shown to be the primary contributor to the HF component of the spectrum through research using muscarinic receptor blockades and vagotomies (Akselrod et al., 1981; Malliani, Pagani, Lombardi, & Cerutti, 1991; Pomeranz et al., 1985). Less clear is the ANS branch

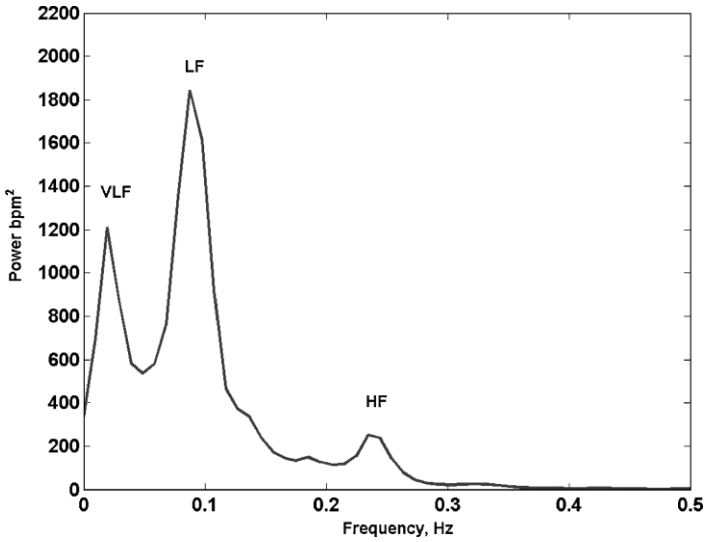


Figure 10: Power spectral analysis of HRV
(de Jong & Randall, 2005)

contribution to the low frequency (LF) component of the spectral analysis. Some research groups suggest that the LF component is indicative of sympathetic activity (Malliani et al., 1991), whereas others argue that it reflects a combination of both sympathetic and parasympathetic components (Kamath & Fallen, 1993; Montano et al., 1994; Rimoldi et al., 1990). It has been suggested that the decrease in absolute power of the LF component during some conditions associated with sympathetic activation, may explain the overall decrease in total spectral power during sympathetically evoked tachycardia (European Society of Cardiology & North American Society of Pacing Electrophysiology, 1996).

Finally, analysis of HRV can provide insight into the physiologic endpoints achieved through autonomic control and perhaps some of the underlying neurophysiologic mechanisms. However, knowing that these neural mechanisms always interact, the interpretation and reporting of HRV findings should avoid definitive claims regarding the unique contribution of either ANS branch to the observed response. In this

light, this analytical tool may be cautiously used to inform our understanding of ANS modulatory changes in cardiac function resulting from various disease- and treatment-states.

1.2.3.5 Quantitative Sudomotor Axon Reflex Test

Controlled by the sudomotor-sympathetic branch of the ANS, sweating is the primary mechanism used by our bodies to dissipate heat. Thermoregulation is an ANS-mediated process that is vital not only to our ability to carry out our activities of daily living (Duncan, Howley, & Johnson) but also to our survival. To maintain our body temperature within normal homeostatic limits, we rely on continuous input from central and peripheral thermoreceptors. These thermoreceptors, located in the preoptic anterior hypothalamus, spinal cord, skin and viscera, transmit neural messages to the hypothalamic-thermoregulatory center for integration and processing (Low, 2004; Schmidt & Chan, 1992). Depending on the type of afferent information, the thermoregulatory center will respond with the appropriate efferent reflex response, activating pathways meant to either conserve and create or dissipate heat. When appropriate, the hypothalamus initiates the sweat response by sending efferent signals to the periphery via the preganglionic cholinergic neurons. Synapsing in the paravertebral ganglia, and triggered by the release of acetylcholine, depolarization of the postganglionic axon stimulates the eccrine glands (M_3 muscarinic receptors) to evoke a sweat response (Low, 2004; Schmidt & Chan, 1992). Functionally, this sweat response acts to cool down the body through evaporative heat loss, the most efficient form of “in air” heat dissipation.

Clinically, sudomotor function assessments have been shown useful in localizing, diagnosing and monitoring the progression of neurologic disorders resulting from ANS

insufficiency. One such sudomotor assessment is called the Quantitative Sudomotor Axon Reflex Test (QSART). In each of the four tested QSART sites (medial forearm, proximal lateral leg, distal medial leg, and proximal lateral foot), the normal afferent and efferent reflex information are relayed along the ulnar, peroneal, saphenous and sural nerves, respectively. A multicompartmental sweat cell is placed at each site. Bypassing

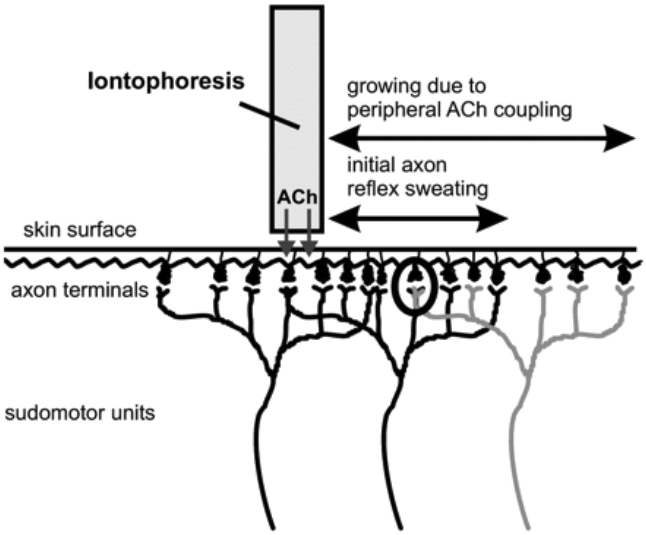
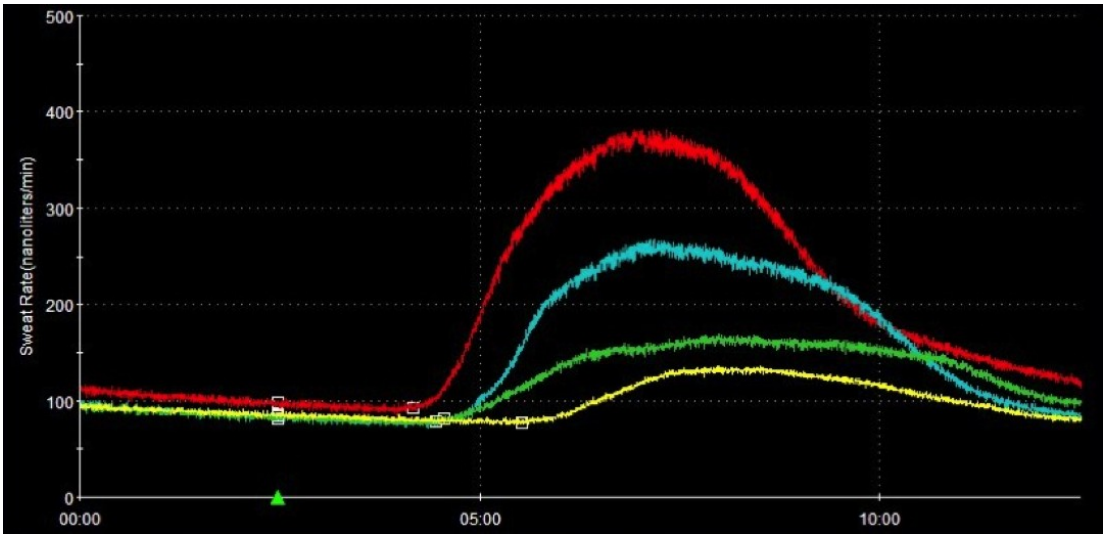


Figure 11: Acetylcholine-mediated iontophoresis (Schlereth, Brosda, & Birklein, 2005)

the central and preganglionic neural components, using a constant current generator, acetylcholine iontophoresis triggers a postganglionic axon reflex-mediated sweat response (**Figure 11**). The sweat response is measured through the quantification of humidity changes in the air being passed through the capsule. The site-specific, analyzed components of this reflex response are total volume, baseline volume, response latency and ending offset volume. The volume components are evaluated and determined to be either i) normal, ii) reduced, iii) absent, iv) excessive or v) persistent.

Normal Response



Abnormal Response

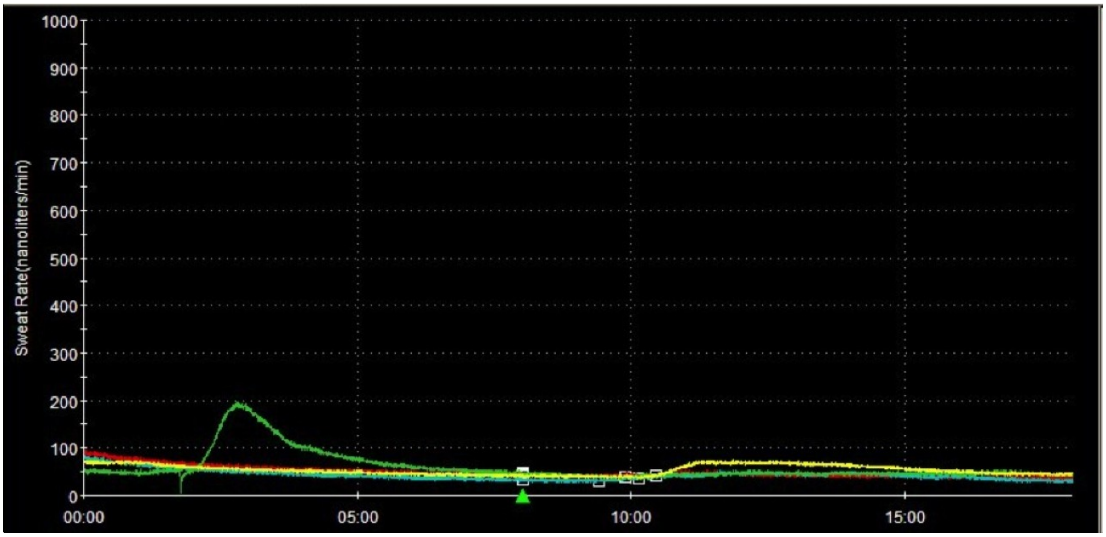


Figure 12: Normal and abnormal postganglionic sudomotor sweat responses (Clinic data – Schondorf, 2013)

This evaluation can be used as an indicator of postganglionic sudomotor integrity and has been shown to be sensitive and reproducible in the testing of diabetics and controls (Hoitsma et al., 2004). One of the previously described limitations of using QSART to evaluate the integrity of the entire sweat response is that it only measures postganglionic sudomotor responses and is unable to identify preganglionic lesions (Illigens & Gibbons,

2008). Compared to other sweat tests (i.e. Thermoregulatory Sweat Test), the QSART is likely best suited to our purposes because it is well tolerated, requires less time to perform, can help to localize lesions to either pre or post-ganglionic and has fewer confounders (Fealey, 1997).

Regardless of the mechanism of damage, impairment of this sudomotor axon reflex response may place individuals affected at an increased risk of heat injury due to their inability to dissipate body heat. In the context of cancer and cancer rehabilitation, disease or treatment-related thermoregulatory impairment may similarly predispose patients to heat injury and poorer exercise tolerance.

1.2.3.6 Autonomic Assessment Summary

Although other ANS-mediated cardiovagal, adrenergic and sudomotor challenges exist, the aforementioned autonomic challenges were the best suited to our testing purposes. In each case, the specific tests and protocols were chosen on the basis of patient tolerance, reproducibility and their complementary contributions to a broader understanding of autonomic responsiveness. Furthermore, these challenges are commonly used in a clinical battery of ANS challenges and analysed using the Composite Autonomic Scoring Scale (CASS) (Low, 1993b).

Following the completion of all four autonomic challenges, the response data are compiled and divided into three component indices (cardiovagal, adrenergic and sudomotor). The component score for the cardiovagal index is based on the magnitude of the HR response to RSA and the VM (otherwise known as the Valsalva Ratio (VR)). The adrenergic index is based on the BP response to Phase II and Phase IV of the VM and the BP response to heads-up tilt. The sudomotor index is based on the volume and

pattern of the sweat response to QSART. As stated previously, interpretations of indirect physiologic measurements are prone to error, especially in the context of single ANS challenges being analyzed and interpreted in isolation. As such, CASS was created to help provide a global assessment of ANS responsiveness. The cardiomotor, vasomotor and sudomotor responses to each challenge provides complementary pieces of information that speak to the integrity of each CASS component. The combined responses within each component score are then graded based on the severity of abnormality (mildly, moderately or severely abnormal).

We anticipate that the study of ANS function in AYAs will have several important methodological and theoretical benefits. First, given the heterogeneity of cancer patients (diagnoses and treatments), it is essential that other known autonomic testing confounders be well controlled. AYAs are expected to not be as likely to experience age and comorbidity related declines in ANS reflex responsiveness. This assumption applies to both the patient and control groups. As discussed in **Section 1.5.5.2**, previous cancer-ANS research has been confounded by the inclusion of subjects with known CV, metabolic and NS comorbidities. Knowing that indirect ANS assessment alone cannot differentiate between effector organ and autonomic dysfunction, the findings of such studies are questionable. Second, the voluntary subject performance instructions may be better understood and adhered to than in a younger population. Third, the majority of AYA cancer patients will survive many years following their treatments. Knowing that they are at an increased risk of CVD development, exercise interventions may be useful in controlling said risk. However, ANS function is known to play an important role in regulating human exercise responses. As such, cancer and treatment-related ANS damage may result in exercise intolerance, thus limiting its potential benefits.

1.3 Cardiovascular Response to Acute Exercise

1.3.1 Basic Cardiovascular Structure and Function

ADL primarily require aerobic, or O_2 dependent, work. An individual's ability to perform this type of work is contingent on the efficiency of the O_2 transport (blood flow) and consumption (mitochondrial) systems. The O_2 transport system is multifaceted. Coordinated by central, peripheral and neuro-hormonal components of the ANS, its overall efficiency is dependent on the synergistic action of the heart, lungs and circulatory vessels (arteries, veins and capillaries). The CV and musculoskeletal reserve capacities (CVRC and MSRC, respectively) are barely taxed during ADL in healthy individuals (Fletcher et al., 2001). However, these reserve capacities can be greatly reduced in various disease- and deconditioning-states, thus requiring a larger proportion of an afflicted individual's maximal capacity to carry-out their ADL (Hagberg, 1994). This increased exertion is both mentally and physically draining, and serves as a deterrent to maintaining activity levels.

1.3.2 Assessment of Cardiovascular Function

1.3.2.1 Maximal and Submaximal Exercise Testing

Maximal exercise (ME) tests have been shown to be valid and reliable measures of physiological function, such as O_2 uptake (VO_2) and consumption in skeletal muscle and pulmonary function (Fletcher et al., 2001; Shephard et al., 1968). Exercise response is maximal when O_2 uptake (VO_{2max}) does not increase despite further increases in workload (Fletcher et al., 2001; McArdle et al., 2007). The actual VO_{2max} that can be attained reflects the delivery capacity of the O_2 transport system and the efficiency with which O_2 is taken up and utilized by working muscles (Hartung, Krock, & Crandall, 1993). These tests are typically performed on a treadmill or a stationary bicycle. ME

methodology described above stands in stark contrast to submaximal exercise (SME) tests that rely on predictive equations or extrapolations from physiologic relationships (Shephard et al., 1968). ME testing in special populations, such as ours, may not be well tolerated for a variety of reasons, including: i) likelihood of pre-VO_{2max} fatigue and increased motivational requirement (Noonan & Dean, 2000), ii) incidence cancer-related fatigue (Curt et al., 2000) and neuromuscular complications (Chen, Jungsuwadee, Vore, Butterfield, & St. Clair, 2007) and iii) the diminished efficiency of the O_2 transport system (Macvicar, Winningham, & Nickel, 1989). Accordingly, the use of SME testing protocols may be more appropriate. In fact, research has shown that ME testing may be contraindicated or of little use in a population afflicted with cardiopulmonary, neuromuscular or musculoskeletal impairments (Noonan & Dean, 2000). The measures of interest in ME testing are used for either diagnostic purposes or in the evaluation of treatment outcomes, but the intensity of testing protocols pose a greater relative risk to the subjects. Given the difficulty predicting and managing this risk, when testing extremely heterogeneous patient groups, SME testing protocols should be used to safely and reliably predict or assess the following outcomes: i) the extent of disease or treatment-related damage, ii) VO_{2max}, iii) the outcome of therapeutic interventions like exercise programs, iv) functional outcomes and v) in making diagnoses (A.C.S.M., 1995; Hagberg, 1994; Noonan & Dean, 2000).

1.3.2.2 Sources of Error

Both ME and SME testing have known sources of error. In ME testing, there are inconsistencies in the determination and reporting of VO_{2max} data. Duncan, Howley & Johnson (1997) suggested that it is insufficient to use of VO_2 plateau as the defining criteria for the achievement of VO_{2max}. Their findings, consistent with the literature, revealed the attainment of a VO_2 plateaus were only indicative of maximal effort in 50%

or less of the subjects assessed using continuous protocol methodology, and 60 – 90% reached a plateau using the discontinuous protocol (Duncan et al., 1997). Additionally, during a ME test, if the aforementioned VO_{2max} criteria are not met, the term used to describe the achieved VO_2 level should be "VO_{2peak}" (Zeballos & Weisman, 1994). In fact, Zeballos and Weisman (1994) suggested that few individuals actually achieve their true VO_{2max} and that VO_{2peak} values are frequently mistakenly reported as VO_{2max} values. In a population of healthy individuals with good cardio-pulmonary function, the day-to-day variation of intra-individual VO_{2max} values has been reported to differ by 4% to 6% (Noonan & Dean, 2000). Furthermore, in populations with cardiopulmonary impairment, such as chronic obstructive pulmonary disease (COPD), the day-to-day intra-individual VO_{2max} variation is described as differing by 6% to 10% (Noonan & Dean, 2000). Additional drawbacks or weaknesses in using ME tests are: i) if the subject isn't able to achieve their VO_{2max} without fatiguing first or succumbing to musculoskeletal complications, then the test results are invalid; ii) much higher levels of motivation are required by the subject; iii) they require additional and more sophisticated monitoring equipment, medically trained staff and are more laborious (Noonan & Dean, 2000).

As mentioned previously, SME tests use an indirect or predicted method of determining an individual's VO_{2max}. This predictive methodology is physically less demanding than ME tests, but its use introduces an additional source of error. Like any indirect method of measurement, SME testing relies on predictive equations to extrapolate from sub-maximally derived values in an attempt to predict maximal values (Jones, Eves, Haykowsky, Joy, & Douglas, 2008). The potential sources of error for this testing protocol include, but are not exclusive to: i) underestimation of VO_{2max} with a very heavy work load due to greater relative increase in VO_2 compared to HR; ii) failure to account for age in a mixed cohort of younger and older subjects, with the "within age

group" SD for maximal HR reported to be ± 10 bpm; iii) erroneous prediction of VO_2 from workload due to a failure to account for varying mechanical efficiencies; and iv) erroneous prediction of VO_2 from HR due to individual variation, potentially due to the training effect where well-trained individuals are usually overestimated and untrained individuals are usually underestimated (Cink & Thomas, 1981; Fleg et al., 2000; Legge & Banister, 1986; Patton et al., 1982).

1.3.2.3 Exercise Test Selection

Although the reported incidence of adverse events are relatively low in both ME and SME, SME assessments are safer and a more tolerable means of CV evaluation. The choice of test should stem from the careful consideration of what parameters the study is trying to assess. The most appropriate exercise challenge tests should be as undemanding as possible yet strenuous enough to induce the CV adaptations desired and should have a normative performance index through which comparisons could be made. The current study involves the assessment of a population of, otherwise healthy, AYA cancer patients. We intend to track changes in their functional performance status over time. In a population with virtually no confounding comorbidities, typical functional assessments, like the 6-minute walk test, may not present enough of a challenge to discern changes in functional status. However, for patients in the midst of chemotherapy treatment protocols, ME testing may impose too high a demand on individual energy reserves and, in the long run, may discourage participation in the study (Noonan & Dean, 2000). These factors essentially limit the testing options to a SME protocol.

After much consideration, the modified Astrand-Rhyming cycle ergometry protocol emerged as the best fit for this project. This CV challenge has been used extensively in both epidemiological (Andersson, 2004; Siconolfi, Cullinane, Carleton, &

Thompson, 1982) and clinical studies (Hagberg, 1994; Hartung, Blancq, Lally, & Krock, 1995). Furthermore, there were no reports of intolerance or serious adverse events (AE) when this protocol was used to test a similar population of AYA cancer patients (Thorsen et al., 2006; Thorsen et al., 2005). The test itself provides a performance outcome-based categorization through which performance trends can be established (Bailey, Shephard, Mirwald, & McBride, 1974) and has age- and sex-matched normative value sets to which our subjects can be compared (Bailey et al., 1974).

1.4 Autonomic and Heart Function in Health and Disease: The Role of Exercise

The inherent difficulty in defining the relationship between autonomic function and CV health lies in the limitations of assessment techniques. Investigations of human autonomic function rely on the non-invasive quantification of ANS-controlled effectors. In every case, aberrant findings may be attributable to either effector organ or ANS damage. Therefore, in the absence of pan-dysautonomia, the correct interpretation and characterization of subtle changes elicited by any single ANS challenge is impossible.

Previous CVD-ANS research has attempted to define causal, predictive and prognostic relationships. Due to the aforementioned limitations with ANS testing, no definitive relationship has been established. However, therapeutic exercise training has been shown to improve common indices of CV and ANS function in multiple CVD populations. Given that cancer patients receiving chemotherapy are considered within the Stage A heart failure group (among the highest risk for developing CVD) (Bonow et al., 2005), engaging in regular exercise may have important protective benefits in this population. We acknowledge that it is impossible to discern whether the benefits

described in the following review are related to changes in either the CV effectors or the ANS's control of. However, for the purposes of this review, common indices of CV and ANS function are referred to in the context with which they were presented (in the literature). Regardless of their relationship, the exercise-related improvements in these common indices preserve their importance.

1.4.1 Introduction

In recent years, evidence has emerged highlighting the potential influence of autonomic function in health, disease, as well as in the emerging role of therapeutic CV exercise to preserve and restore it. Drawing from important reviews articles, the following is a condensed review of the evidence supporting the use of exercise to restore autonomic function and, by doing so, improve or prevent associated CV morbidity and mortality (Rosenwinkel et al., 2001; Thayer & Lane, 2007).

Inherent to our survival is the physiologic predisposition toward energy conservation (reflected in our resting circadian HR fluctuations and exercise-induced HR training adaptations). In health, dynamic modulation of energy expenditure is achieved through the synergistic influence of both ANS branches wherein parasympathetic influences dominate at rest. A common trait of pathology is the loss of this systemic compliance, and therein the capacity to adjust to dynamic metabolic needs and environmental stimuli. This systemic rigidity has been associated with morbidity and mortality (Lipsitz & Goldberger, 1992; Peng et al., 1994). Characterized by sympathetic dominance, either through vagal withdrawal or sympathetic hyperactivity, prolonged ANS imbalance has been ascribed to the development of a variety of chronic comorbidities (Rosenwinkel et al., 2001; Thayer & Lane, 2007).

1.4.2 Influence of Exercise on Healthy Autonomic and Heart Function

Exercise studies, using both pharmacological blockade (SNS and PNS), HRV indices (PNS) and circulating catecholamine measurements (SNS), have played an important role in helping us understand the influence of both branches of the ANS in modulating our acute response to exercise.

During exercise, the initial HR response (up to a HR of 100 beats per minute (bpm)) is primarily influenced by vagal withdrawal (Arai et al., 1989; Goldsmith, 1991; Robinson, Epstein, Beiser, & Braunwald, 1966; Rowell, 1993) with sympathetic modulation playing a larger role in moderate and heavy exercise adaptations (Christensen & Brandsborg, 1973; Orizio et al., 1988; Robinson et al., 1966; Rowell, 1993). Conversely, following an acute bout of exercise, early HR recovery is thought to be largely influenced by parasympathetic reactivation with sympathetic withdrawal contributing more to later recovery (Imai et al., 1994; Ohuchi et al., 2000; Pierpont, Stolpman, & Gornick, 2000; Sears, Choate, & Paterson, 1998).

Through a combination of intrinsic and systemic mechanisms, regular CV exercise has a profound and well-documented impact on decreasing resting and training HR and improving HR recovery from acute bouts of exercise. It is possible that ANS-mediated pathways account for much of the systemic influence on these parameters. Studies investigating the impact of regular exercise training on resting HR and ANS function have identified that, compared to matched sedentary controls, resting parasympathetic activity levels are higher in endurance-trained athletes (Barney et al., 1988; Dixon et al., 1992; Goldsmith et al., 1992a), middle-aged and older men (De Meersman, 1993; Seals & Chase, 1989) and physically active post-menopausal women (Davy, Miniclier, Taylor, Stevenson, & Seals, 1996). These finding have been

corroborated by longitudinal ANS-exercise studies of younger (De Meersman, 1992), middle-aged (Seals & Chase, 1989) and older individuals (Levy et al., 1998; Stein, Ehsani, Domitrovich, Kleiger, & Rottman, 1999). It has also been demonstrated that, at any given workload, trained individuals have reduced sympathetic activity (Hartley et al., 1972; Lehmann, Schmid, & Keul, 1984). Finally, it is also well established that endurance-trained individuals recover faster from exercise than their untrained counterparts (Hagberg, Hickson, Ehsani, & Holloszy, 1980; Hagberg, Hickson, McLane, Ehsani, & Winder, 1979; Imai et al., 1994).

1.4.3 Autonomic Dysfunction in Cardiovascular Disease

Characterized by the aforementioned loss of dynamic autonomic control, pathologic perturbations of autonomic function have been shown to manifest in a variety of ways, including decreased HRV at rest (Dekker et al., 2000; Ziegler, Laude, Akila, & Elghozi, 2001), circadian HRV perturbations (Cygankiewicz, Krzysztof Wranicz, Bolinska, Zaslonka, & Zareba, 2004; Korpelainen, Sotaniemi, Huikuri, & Myllyla, 1997), high resting HR (Levy, 1990; Uijtdehaage & Thayer, 2000) and poor HR recovery from exercise (Shetler et al., 2001). Keeping in mind that these indices could either reflect effector organ or ANS dysfunction, as prognostic indicators, these clinical markers have all been strongly associated with increased risk of morbidity and mortality (Cole, Blackstone, Pashkow, Snader, & Lauer, 1999; Cole, Foody, Blackstone, & Lauer, 2000; Dekker et al., 2000; Ershler & Keller, 2000; Gibbons, 2002; Habib, 1999; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Nishime, Cole, Blackstone, Pashkow, & Lauer, 2000).

1.4.4 Role of Exercise in Preserving or Restoring Autonomic Function

As previously discussed, autonomic dysfunction may be associated with the greater risk of disease development, severity and mortality from a multitude of CV and

metabolic sequelae. Pharmacological studies of affected animals (Hull et al., 1994; Schwartz et al., 1988; Vanoli et al., 1991; Zuanetti, De Ferrari, Priori, & Schwartz, 1987) and large human trials (T. B. B. H. A. T. R. Group, 1982; T. N. M. S. Group, 1981; Hjalmarson et al., 1981; Packer et al., 1996) have demonstrated that the improvements in HRV (an important marker of autonomic and CV health) are associated with decreases the related morbidity and mortality risks. Similarly, human exercise training studies have clearly demonstrated exercise's potential to improve HRV following myocardial infarction (La Rovere, Mortara, Sandrone, & Lombardi, 1992; Malfatto et al., 1996; Malfatto et al., 1998; Oya, Itoh, Kato, Tanabe, & Murayama, 1999; Schwartz, La Rovere, & Vanoli, 1992), heart surgery (Iellamo, Legramante, Massaro, Raimondi, & Galante, 2000) and in those with congestive heart failure (Adamopoulos et al., 1995; Belardinelli, Georgiou, Cianci, & Purcaro, 1999; Coats et al., 1992; E. H. F. T. Group, 1998; Keteyian et al., 1999; Kiilavuori, Naveri, Leinonen, & Harkonen, 1999; Kilavuori, Toivonen, Naveri, & Leinonen, 1995).

In summary, pathologic perturbations to the ANS that disrupt its dynamic control mechanisms are associated with increased risk morbidity and mortality. Pharmacologic- and exercise-based interventions of affected individuals have been shown to improve prognostic and functional patient outcomes and decrease the associated morbidity and mortality risks. It may therefore be plausible that CV exercise training play a similar role in improving cancer-related autonomic dysfunction or indices of.

1.5 Impact of Cancer on Autonomic and Cardiovascular Function

As in Section 1.4, we similarly acknowledge that the disease- and treatment-related damage to the autonomic or CV systems, reported below, may be due to either effector organ or ANS dysfunction.

1.5.1 Introduction

Relatively few studies have looked at the impact of cancer and chemotherapy on autonomic function. In the context of cancer rehabilitation, further investigation is warranted to help us understand the disease- and treatment-related impacts on CVRC. A review of the related literature reveals a number of mechanisms of autonomic and CV damage, which are likely to result in the impairment of patients' CVRC and the potential for exercise-based therapeutic interventions.

1.5.2 Impact of Cancer on Autonomic Function

Cancer has been shown to have direct and indirect effects on the NS (Falah, Schiff, & Burns, 2005). In their 2005 review, these authors identified a myriad of neuropathies (i.e. radiculopathies and plexopathies) resulting from the metastatic invasion of nervous tissue by malignant cells or from direct compression caused by the growth of an adjacent tumour. In either case, the severity of the symptoms and their functional relevance were associated with the locus and the overall size of the malignant growth (Falah et al., 2005). An indirect pathway of malignant NS damage stems from the development of paraneoplastic and paraproteinemic syndromes. These remote effects of cancer are not due to the primary tumour, metastatic disease, or treatment related abnormalities; rather, they are the result of an autoimmune response targeting a tumour's neural antigens (Anderson, Cunningham, & Posner, 1987; Graus et al., 2004;

Levin, 1997; Pittock, Kryzer, & Lennon, 2004). Symptoms related to these syndromes often present as early as two years in prior to those related to the cancer itself (Anderson et al., 1987).

Paraneoplastic syndromes most commonly occur in patients with small cell lung cancer, or cancers of the pancreas, testis, breast and gynaecological cancers (Rojas-Marcos et al., 2003; Rudnicki & Dalmau, 2000). In an earlier investigation of autonomic function in twenty patients with lymphoma, baseline ANS evaluations demonstrated 80% of patients had subclinical ANS dysfunction, with 55% of patients experiencing persistent dysfunction post treatment (Turner, Boland, Parker, & Ewing, 1993). Consistent with the current literature (Darnell & Posner, 2003), the authors cited the probable influence of a paraneoplastic immune response as the cause of the baseline ANS dysfunction. Interestingly, despite the use of known neurotoxic chemotherapy agents, they reported significant improvements in ANS function post treatment (Turner et al., 1993).

1.5.3 Impact of Cancer on Cardiovascular Function

To the best of our knowledge, and with the exception of the previously described paraneoplastic influence, there are no published accounts of the impact of cancer on SME capacity, as indicated by SME testing, in any age group. Reason suggests that any malignancy, which directly compromises cardiac, lung, vascular, or neuromuscular functioning, may directly impact an individual's physical work capacity. The severity of the complications associated with the growth of a tumour in any of the aforementioned locations would primarily depend on the extent of the local invasion.

1.5.4 Chemotherapy: Mechanisms, Risks and Limitations

Chemotherapy is aggressively used as a frontline defence against tumour

proliferation and metastasis in most cancer patients and is often used in concert with radiotherapy or surgical interventions. To provide increased efficacy, chemotherapeutic treatment strategies often include the synergistic use of multiple agents (drugs). These agents predictably differ in their mechanisms of action and are categorized into families based upon their pharmacodynamic mechanisms. Collectively, these agents disrupt cancer cell proliferation and metastases through the following pathways: i) anti-metabolic activity, ii) inhibition of DNA mediated transcription and replication, iii) inhibition of gene expression, iv) destruction of tumour cell DNA, v) inhibition of enzymatic function, vi) induction of apoptosis, vii) growth arrest, viii) disruption of membrane systems and trans-membrane molecular transport and ix) the suppression of microtubule dynamics (Abal, Andreu, & Barasoain, 2003; Cepeda et al., 2007; Furlanut & Franceschi, 2003; Genestier, Paillot, Quemeneur, Izeradjene, & Revillard, 2000; Hande, 1998; Hideo, 1970; Katzung, 1995; Longley, Harkin, & Johnston, 2003; Siegfried, Kennedy, Sartorelli, & Tritton, 1983). An inherent drawback to the use of chemotherapy is the non-cell and non-cell cycle specific nature of its effect. Once administered, these drugs act systemically and target both healthy and cancerous cells alike. Damage to healthy cells may manifest in several ways including nausea, vomiting, hair loss, cardiotoxicity, neuropathy and bone marrow suppression. Provided the affected cells have mitotic capabilities, the resulting damage may be temporary. However, there remain a multitude of problems and concerns surrounding the adverse side effects caused by these toxic interventions, including potentially life-threatening organ dysfunction and failure. Research has shown a distinct cumulative and dose-dependent symptom response associated with chemotoxicity (Doroshow, Locker, & Myers, 1980; Falah et al., 2005; Giantris, Abdurrahman, Hinkle, Asselin, & Lipshultz, 1998; Joshi et al., 2007; Minotti, Menna, Salvatorelli, Cairo, & Gianni, 2004). The incidence and severity of cardiotoxic and neurotoxic complications differ according to the agent used. See **Appendix B** and **C**

for a detailed overview of known cardiotoxic and neurotoxic agents, respectively. Among the host of affected organs and systems, the heart and its accompanying innervation are particularly susceptible to chemotherapy's toxic effects (Aleman et al., 2007; Alter, Herzum, Soufi, Schaefer, & Maisch, 2006; Cardinale et al., 2006; Hirvonen, Salmi, Heinonen, Antila, & Välimäkiy, 1989; Jarfelt, Kujacic, Holmgren, Bjarnason, & Lannering, 2007; Kosmas et al., 2008; Myrehaug et al., 2008; Tascilar, Loos, Seynaeve, Verweij, & Sleijfer, 2007; Viniegra et al., 1990; Zver, Zadnik, Černelč, & Koželj, 2008).

1.5.5 Impact of Chemotherapy on Autonomic Function

1.5.5.1 Chemotherapy-Induced Autonomic and Peripheral Neurotoxicity

Of the many tissues susceptible to chemotherapy-induced damage, nervous tissue may be particularly vulnerable. Generally speaking, neurons are classified as post-mitotic tissue and, once mature, are no longer able to replicate themselves. This lack of reproductive capability is significant in that damage to this tissue type has been shown to cause chronic comorbidity, as previously described. Importantly, autonomic neuropathies typically involve damage to small, unmyelinated nerve fibers. Accordingly, chemotherapeutic agents known to damage these small fibers are the most likely disrupt ANS function.

In general, chemotherapy typically causes both large and small fibre neuropathies (Armstrong, Almadrones, & Gilbert, 2005) with autonomic neuropathies typically involving the latter (McLeod & Tuck, 1987). Autonomic neuropathies and impairments have been reported in cancer patients treated with a variety of chemotherapeutic agents, including: i) vincristine (Gomber, Dewan, & Chhonker, 2010; Legha, 1986), ii) cisplatin (Boogerd, Bokkel Huinink, Dalesio, Hoppenbrouwers, & Sande, 1990; Hansen, 1990), iii) paclitaxel (Ekholm, Rantanen, Antila, & Salminen,

1997; Ekholm et al., 2000), iv) gemcitabine (Dormann, Grunewald, Wigginghaus, & Huchzermeyer, 1998) and v) doxorubicin (DOX) (Hrushesky et al., 1991; Viniegra et al., 1990). Furthermore, most of these compounds have been shown to accumulate in key autonomic regions, disrupt axon transport, interfere with microtubule assembly and function, cause demyelination and damage nervous support cells (Armstrong et al., 2005; Quasthoff & Hartung, 2002). These chemotherapeutic agents are among the most commonly used in the treatment of AYA cancers.

1.5.5.2 Autonomic Testing During and Post Chemotherapy

The majority of autonomic evaluations completed thus far have assessed cardiovagal or adrenergic function utilizing the test battery described by Ewing and Clarke (Ewing & Clarke, 1986) with only one studying assessing sympathetic-mediated sweat function as described by Shahani (Shahani, Halperin, Boulu, & Cohen, 1984).

Short term and circadian changes in HRV are known risk factors for CV disease (CVD) and all-cause mortality (Huikuri et al., 1994; Thayer & Lane, 2007). Using both RSA and 24-hour recordings, diminished HRV has been reported in patients treated with vincristine (Hirvonen et al., 1989), paclitaxel (Ekholm et al., 2000), DOX (Hrushesky et al., 1991), as well as patient groups treated with various combination therapies (Hansen, 1990; Turner et al., 1993). Aberrant BP variability and maladaptive orthostatic responses have been observed in patients treated with paclitaxel, taxanes, vinca alkaloids and cisplatin (Ekholm et al., 1997; Jerian et al., 1993; Quasthoff & Hartung, 2002). The assessment of sympathetic-mediated sweat function found a prolongation of the skin response latency at both the hand and foot (Argyriou et al., 2005).

Unfortunately, the methodology and reporting from these trials were inconsistent. Despite the frequent use of the protocol described by Ewing and Clarke, these studies lacked sufficient consistency in the selection and execution of their autonomic challenges, in the application of their eligibility and test criteria and many failed to include key methodological detail required to compare between trials. As such, there remains insufficient evidence to make any conclusions regarding the presence or nature of cancer-related autonomic dysfunction.

1.5.6 Impact of Chemotherapy on Cardiovascular Function

Stated previously, cancer patients receiving chemotherapy are considered within the Stage A heart failure group (among the highest risk for developing CVD) (Bonow et al., 2005). Despite improvements in screening techniques, drug administration and the use of cardio-protectant strategies, the introduction of new targeted anticancer drugs (also cardiotoxic), coupled with improved patient survival and an aging population increases the significance of cancer-related CV toxicity (Monsuez, Charniot, Vignat, & Artigou, 2010; Senkus & Jassem, 2011). The growing recognition and understanding of cancer-related CV toxicity has lead to a merging of medical disciplines, now referred to as cardio-oncology (Albini et al., 2010). Recent reviews on the subject have extensively covered the pathophysiologic mechanisms underlying the various drug-related CV toxicities (congestive heart failure, myocardial infarction, myocardial ischemia, hypotension, hypertension, arrhythmias, metabolic, and thrombotic complications) and presenting symptoms (Monsuez et al., 2010; Senkus & Jassem, 2011).

Chapter II

Rationale and Clinical Significance

Despite therapeutic advances, cancer patients remain at risk of developing a host of disease- and treatment-related CV and metabolic morbidity, as compared to their peers. Emerging evidence in related fields has begun to establish links between the loss of dynamic autonomic control and risk/severity of CV sequelae and mortality. Regular CV exercise training has been shown to improve multiple prognostic and functional patient outcomes associated with autonomic and CV health, and, in doing so, may be effective in improving related outcomes for cancer patients. A relationship between cancer and CVD is evident. What is less clear is why cancer patients appear to be more susceptible to developing CVD. Multifactorial in nature, the development of these life-altering conditions is likely influenced by complex interactions between behavioural, genetic, and environmental factors coupled with disease- and treatment-related damage to patients' effector organs and systemic physiology.

One possible explanation for the cancer-related increase in CVD development risk may be the effect of cancer and anticancer therapy on ANS function. This relationship is well supported in the literature but has yet to be clearly defined. The ideal launch point for this investigation requires study within the AYA cancer population for two reasons. First, ANS function is easily perturbed, known to decline with age and be influenced by existing comorbidities. AYA cancer patients, however, are the most likely to have good ANS reflexes as they are young and relatively unaffected by comorbidities. Second, in comparison with older cancer patients, the premature development of CVD in AYA cancer survivors affects many more years of life per individual. The implication of this carries significant personal and societal burden.

The general aim of this study was to establish the feasibility of testing autonomic and CV function in AYA cancer patients undergoing treatment for cancer by: i) defining the methodological pitfalls and best-practice criteria for ANS testing in cancer, and ii) providing initial physiologic evidence of autonomic perturbations in cancer patients using the CASS. As previously mentioned, ANS function may be perturbed by cancer and anticancer therapies. However, given the heterogeneity of the population (Dx and treatments) and the complexity of the reflex responses, ANS testing during cancer treatment may not provide reliable evidence of ANS function. Accordingly, the significance of this study is to define key methodological parameters required to study ANS function in patients undergoing a variety of chemotherapy protocols, for the purposes of launching future investigations. If successful, we intend to continue this line of investigation in an effort to verify the occurrence of cancer-related ANS damage, and, if warranted, track the pathogenesis of these complications in an effort to define the relationship between autonomic mechanisms underlying the development of CVD in cancer survivors.

Chapter III

Research Objectives and Hypotheses

The purpose of this study was to assess the feasibility of conducting concurrent ANS and CV evaluations in AYA cancer patients undergoing treatment for various cancers. Our objectives were to i) identify the methodological pitfalls of autonomic testing in cancer, ii) define best-practice criteria for the future testing of autonomic function in cancer, and iii) provide initial physiologic evidence of autonomic perturbations in cancer patients using the CASS. In keeping with recent pilot study design and reporting guidelines (Thabane et al., 2010), we crafted this research project to reflect the requirements of a similar, larger scale investigation.

Our primary research question was: Does cancer or chemotherapy have a significant impact on autonomic nervous function in AYA cancer patients at rest? Our primary research hypothesis was that, AYA cancer patients would demonstrate a significant decrease in ANS function (as indicated by the CASS) after receiving chemotherapy.

Our secondary research question was: If identified, does cancer or chemotherapy-related autonomic dysfunction impair exercise tolerance of AYA cancer patients to, in, and in recovery from a brief SME challenge? Our secondary research hypothesis was: If present, chemotherapy-related autonomic dysfunction would significantly impair the exercise response of AYA cancer patients to, and in recovery from, a brief SME challenge.

Chapter IV

Assessing the Impact of Cancer and Chemotherapy on Autonomic Function and Cardiovascular Reactivity in Young Adults with Cancer: A Feasibility Study

Introduction

Despite therapeutic advances, cancer survivors remain at risk of developing a host of disease- and treatment-related cardiovascular (CV) and metabolic morbidities (Albini et al., 2010; Demark-Wahnefried et al., 2005; Monsuez et al., 2010; Oeffinger et al., 2010; Senkus & Jassem, 2011). Emerging evidence in related fields has begun to establish links between autonomic nervous system (ANS) impairment (as evidenced by short term and circadian changes in heart rate (HR) variability (V)) and increased risk/severity of CV disease (D) and all-cause mortality (Cole et al., 1999; Cole et al., 2000; Dekker et al., 2000; Ershler & Keller, 2000; Gibbons, 2002; Huikuri et al., 1994; Kiecolt-Glaser et al., 2002; Nishime et al., 2000; Thayer & Lane, 2007). Using both short duration and 24-hour recordings, diminished HRV has been reported in patients treated with vincristine (Hirvonen et al., 1989), paclitaxel (Ekholm et al., 2000), DOX (Hrushesky et al., 1991), as well as patient groups treated with various combination therapies (Hansen, 1990; Turner et al., 1993). Aberrant blood pressure (BP) variability and maladaptive orthostatic responses have been observed in patients treated with paclitaxel, taxanes, vinca alkaloids and cisplatin (Ekholm et al., 1997; Jerian et al., 1993; Quasthoff & Hartung, 2002). The only assessment of sympathetically-mediated sweat responses identified a prolongation of the response latency at both the hand and foot (Argyriou et al., 2005). Unfortunately, the methodology and reporting from these trials were inconsistent. Despite the frequent use of the protocol described by Ewing and Clarke, these studies lacked sufficient consistency in the selection and execution of their

autonomic challenges, in the application of their eligibility and test criteria and many failed to include key methodological detail required to compare between trials. As such, there remains insufficient evidence to make any conclusions regarding the presence or nature of cancer-related autonomic dysfunction.

Interestingly, regular CV exercise training has been shown to improve HRV (an important marker of autonomic and CV health) in various CVD populations (Adamopoulos et al., 1995; Belardinelli et al., 1999; Coats et al., 1992; E. H. F. T. Group, 1998; Iellamo et al., 2000; Keteyian et al., 1999; Kiilavuori et al., 1999; Kilavuori et al., 1995; La Rovere et al., 1992; Malfatto et al., 1996; Malfatto et al., 1998; Oya et al., 1999; Schwartz et al., 1992). As such, this type of therapeutic exercise may be effective in improving similar CV outcomes in cancer patients. A relationship between cancer and the development of CVD is evident. What is less clear is why cancer patients appear to be more susceptible to developing CVD. This quandary is unquestionably multifactorial in nature. The development of these life-altering conditions is likely influenced by complex interactions between behavioural, genetic, and environmental factors coupled with disease- and treatment-related damage to patients' effector organs and systemic physiology.

One possible explanation for the cancer-related increase in CVD development risk may be the effect of cancer and anticancer therapy on ANS function. This relationship is often suggested in the literature but has yet to be clearly defined. The ideal launch point for this investigation requires study within the adolescent and young adult (AYA) cancer population for two reasons. First, ANS function is known to decline with age and is influenced by existing comorbidities (Low, 1997). By virtue of their age, AYA cancer patients are the most likely to have normal ANS reflexes as they are young

and relatively unaffected by comorbidities. Second, in comparison with older cancer patients, given their average 5-year survival rates and greater number of years of life ahead of them (Canada, 2012; Ontario, 2006), the premature development of CVD in AYA cancer survivors is likely to account for many more years of life affected per individual. The implication of which carries a tremendous potential burden both to society and thousands of AYAs across Canada.

The purpose of this study was to assess the feasibility of conducting concurrent ANS and CV evaluations in AYA cancer patients undergoing treatment for various cancers. As previously mentioned, ANS function may be perturbed by cancer and anticancer therapies. However, given the heterogeneity of the population (diagnoses and treatments) and the complexity of the reflex responses, ANS testing during cancer treatment may not provide reliable evidence of ANS function. Our additional feasibility concerns included: i) recruitment potential (given that AYAs account for only 10% of cancer diagnoses, and we recruited at time of diagnosis (Dx)), ii) retention rates (anticipated difficulty with compliance and follow-up), iii) capacity to establish a baseline (T1) assessment (variable time between initial Dx and commencement of systemic therapy), iv) performance and tolerability of the ANS and CV test battery components and v) the confounding effects of common symptom-management medications.

Our objectives were to identify the methodological pitfalls of autonomic testing in cancer, define best-practice criteria for the future testing of autonomic function in cancer and, through the use of modern techniques, provide physiologic evidence of autonomic perturbations in AYA cancer patients as a potential precursor to the development of CVD. Accordingly, our research questions and methodology were designed to reflect those to be used in a subsequent, larger investigation of the subject.

Our primary research question was, does cancer or chemotherapy have a significant impact on autonomic nervous function in AYA cancer patients at rest? Our primary research hypothesis was that, AYA cancer patients would demonstrate a significant decrease in ANS function (as indicated by the composite autonomic scoring scale (CASS)) after receiving chemotherapy (Low, 1993b). Our secondary research question was, if identified, does cancer or chemotherapy-related autonomic dysfunction impair exercise tolerance of AYA cancer patients to, and in recovery from, a brief sub-maximal exercise (SME) challenge? Our related hypothesis was, if present, chemotherapy-related autonomic dysfunction would significantly impair the exercise response of AYA cancer patients to, and in recovery from, a brief SME challenge.

Methods

Participants and Setting

We aimed to recruit twenty patients and twenty control subjects matched for sex and age. Initially based on common chemotherapeutic agents within their treatment protocols, patients with newly diagnosed sarcomas, genito-urinary (testicular and ovarian) and gastro-intestinal cancer patients (aged 18-45) were recruited from the AYA Oncology Program of the Jewish General Hospital (JGH), Montreal Quebec. Patients with all stages of disease were eligible provided they had a performance status (ECOG) ≤ 2. *Exclusion criteria*: i) use of any medications, at T1, that interfered with autonomic or CV function, ii) intrinsic cardiac disease or ANS-perturbing comorbidity (e.g., arrhythmia, intraventricular conduction defects, evidence of cardiac ischemia, pre-existing cardiomyopathy, diabetes, hypertension, neuropathy, seizure disorder) and iii) an inability to perform any of the T1 ANS or CV challenges due to tumour location. In accordance with our feasibility objectives, detailed records of recruitment, retention,

testing and confounding drug use were kept. Institutional review boards at both the Jewish General Hospital and Concordia University approved this study.

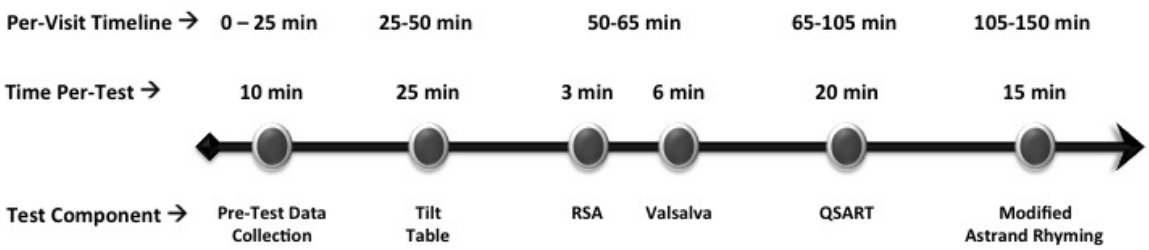
Study Design and Procedure

Subject recruitment took place at the weekly AYA Oncology Program clinic, as well as various other, JGH-based, Segal Cancer Centre oncology clinics. Following an initial appropriate Dx, the investigator obtained medical clearance from the oncologist and then the patient's consent to explain the study. Patients were then given a copy of the informed consent for review and a chance to ask questions. For those agreeing to continue, detailed pre-test instructions were given according to best practices of ANS and CV testing (Jones et al., 2008; Low, 1997). T1 was booked within 24 hours of recruitment. Informed consent was signed at the T1 assessment and in the presence of no less than two study investigators. All patients underwent ANS and CV evaluations at T1 (post Dx and pre-chemotherapy) and follow up ((T2) - between the 4^{th} and 5^{th} chemotherapy treatments).

All procedures were conducted in the Autonomic Reflex Laboratory at the JGH. The non-invasive battery of tests used at rest (respiratory sinus arrhythmia (RSA), Valsalva maneuver (VM), tilt-table and the quantitative sudomotor axon reflex test (QSART)) provided information concerning cardiovagal, sympathetic adrenergic vasomotor and cardiomotor, as well as postganglionic sympathetic cholinergic sudomotor function. The severity and localization of the type and sites of autonomic dysfunction was accurately graded and compared using a validated CASS (Low, 1993a, 1993b). These tests have been routinely performed under clinical and clinical research conditions in patients who were considered to be significantly disabled by diabetes, orthostatic intolerance, chronic fatigue syndrome (Schondorf, Benoit, Wein, & Phaneuf,

1999), or Alzheimer's disease (Schondorf, Benoit, & Chertkow, 2000) in the Autonomic Reflex Laboratory of the JGH for the last 20 years. Immediately following the resting ANS protocol, the subjects were transferred to an adjacent evaluation room to perform a brief, 6-min, SME challenge on a cycle ergometer (Astrand & Ryhming, 1954). The exercise test was proposed to obtain a functional assessment of the indices of CV function (e.g., central (e.g., HRV, HR, stroke volume and cardiac output (CO)) and peripheral (BP and systemic vascular resistance)) that correlate with the ANS testing. Detailed descriptions of the assessments are provided below.

Per-Visit Assessments



'Per-Visit Timeline' includes 'Time Per-Test' and 'Instrumentation/De-Instrumentation Time'.

Figure 13: Sequence of tests

Pre-Test Data Collection

Before each assessment, subject height, weight and current medications were recorded. Subjects also completed the Brief Fatigue Inventory (BFI) and weekly physical activity (PA) MET•hrs•week^{-1} reports.

Autonomic Testing

Cardiovagal and Adrenergic Assessments

HR, finger arterial pressure, end tidal CO_2 were continuously recorded for all cardiovagal and adrenergic autonomic challenges. The measurement devices were

applied pre-test, disconnected during transfer and reconnected. HR was derived from the R-R interval of the surface EKG (*EKG 101 Patient monitor; Biomedical Systems Inc.; St. Louis, MO*), finger arterial pressure measured with a volume clamp photoplethysmograph (*Finometer MIDI Model 2 – b1.0; Finapres; Amsterdam, NL*), and end tidal CO_2 via nasal prongs (*Oximax N-85; Nelicor; St. Louis, MO*) (Halliwill et al., 1997; Whitney, 1953). Cardiac output (CO) was derived from the finger arterial pressure waveform using the pulse contour method (Jellema, Imholz, van Goudoever, Wesseling, & van Lieshout, 1996). These continuous non-invasive measures of CO were able to accurately track relative changes in CO but did not provide accurate measures of actual CO. All analog signals were appropriately sampled at 400 Hz by a computer equipped with an eight-channel A/D acquisition card and software (*WindaqPRO; Dataq; Akron, OH*).

The ANS assessment protocol began with measuring the aforementioned responses for 10 minutes of supine rest followed by 10 minutes of head-up tilt at 80^{o}. The patient was then returned to the supine position. Subsequently the HR response to deep breathing at 6 breaths / min for 10-12 respiratory cycles was measured (Schondorf et al., 1999). The patient then performed two VMs while supine. To perform this manoeuvre the patient blew into a tube and attempted to push a column of mercury to 40 mmHg and maintain that effort for 15 sec (Low, 1993b; Schondorf et al., 1999).

Sudomotor Assessment

The standard test protocol of sudomotor function (sweat gland activity) uses the QSART as a specific measure of postganglionic cholinergic sympathetic sudomotor function (Low, Caskey, Tuck, Fealey, & Dyck, 1983; Low & Opfer-Gehrking, 1992; Low, Opfer-Gehrking, Proper, & Zimmerman, 1990). Measurements were made while the

patient was supine from 4 small multi-compartment sweat cells placed at standard sites (distal forearm, proximal leg, distal leg and foot). Sweating was provoked by 5 minute iontophoresis of 10% acetylcholine (*Iontonphor II Model 6111PM/DX; Life-Tech Inc.; Burlington, ON*). Sweating was recorded for 10 min and expressed as µl/min/cm^2 (*QSWEAT; WR Medical Electronics Company; Maplewood, MN*). During iontophoresis, the patient may experience a tingling or prickling sensation, which was not painful.

Exercise Testing

A brief (6-min) SME test on a bicycle ergometer (*Ergomedic 828E; Monark; Uppsala, SE*) was then performed, using a standardized protocol (Astrand & Ryhming, 1954). After comfortably positioning each subject on the ergometer, HR and BP responses were measured during a 3 min warm-up (no resistance) and work phases (consisted of pedaling against a self-determined, constant load at 50 revolutions / min for 6-7 minutes (HR adaptation-depending)). Rate of perceived exertion (RPE) was collected between the 2nd last and last minute of each work phase. Following this work phase, subjects remained seated upright on the bicycle and continued to pedal (50 revolutions / min with no resistance) for an additional 4 min to ensure a safe and uneventful recovery. Subjects were monitored minute-by-minute and data was recorded (using the aforementioned CV assessment instrumentation) continuously throughout the entire protocol. The workload was selected to elicit heart rates between 120-150 beats/min. This intensity is considered to be light to moderate based upon projected maximal HR reserve values for a population between 18-45 years. This protocol has been followed before without any adverse effects in cancer patients who had recently completed their chemotherapy cycles (Thorsen et al., 2006).

Feasibility Analysis

Accordingly, and in the absence of best-practice guidelines for ANS testing in cancer, we based most decisions for our feasibility criteria (FC) on the combined results of recent, in-treatment, randomized controlled exercise trials in cancer (Adamsen et al., 2009; Courneya et al., 2007; Courneya et al., 2009; Mock et al., 2005) and McGill AYA Oncology Program clinic data (Palumbo & Kavan, 2008). The relevant feasibility endpoints for these trials are summarized in **Table 4**. In attempting to establish our FC, several important factors impacted our decision-making. Previous investigations of ANS function in cancer (Argyriou et al., 2005; Boogerd et al., 1990; Ekholm et al., 1997; Ekholm et al., 2000; Fagundes et al., 2011; Hansen, 1990; Hirvonen et al., 1989; Jerian et al., 1993; Roca et al., 1985; Turner et al., 1993; Viniegra et al., 1990) often had small sample sizes, did not establish pre-treatment baselines, included a wide age-range of participants and lacked sufficient and consistent methodological and results reporting. As such, we had to draw important feasibility information from related, exercise oncology literature. The reviewed exercise oncology trials included comprehensive reports of key methodology, recruitment, trial design and participant flow and, therefore, was often more useful in helping define our FC. The reported averages from these trials (**Table 4**) were combined and listed in **Table 5**. In accordance with Thabane et al. (2010), we established FC that, given that our study did not include an intervention, were more stringent than evidenced in the aforementioned intervention and observation trials (**Table 5**).

Table 4: Relevant Feasibility Endpoints (Exercise Oncology)

	Adamsen et al., 2009	Courneya et al., 2007	Courneya et al., 2009	Mock et al., 2005
Recruitment Period *(months)*	36	30	36	36*
# of Hospitals Involved	2	3	1	4
# Patients Assessed	953	1,468	1,306	234
Ineligible	237	732	620	47
Medical Exclusion *(non-cancer related)*	77	76	NR	NR
Declined Participation	447	494	564	66
# Patients Eligible	269	242	122	121
# Patients Tested @ T1	269	242	122	119
# Patients Retested	235	225	117	108
% Patient Retention	87.4%	93.0%	96.0%	90.8%
# AEs	0	2	3	0
Confounding Medications	NR	NR	NR	NR

* estimated based on reported recruitment period of 1998 & 2001
** details of baseline medical exemptions provided for 2 of 4 studies
NR, Not Reported; T1, Time 1 or baseline

Table 5: Reported vs. Required Feasibility Criteria

Criteria	Reported *(literature)*	Required *(our study)*
1. Recruitment & Access		
1.i: T1 CV or NS Morbidity & Medication Use	6.3%	< 5%
1.ii: Patient Identification *(avg. per hospital, per year)*	26.2	≥ 40
2. Patient Retention Rate *(based on willingness and ability to participate and completion of T2 assessment)*	91.8%	> 95%
3. Pre-Chemo Baseline		
3.i: Number days between Dx& T1	67% Pts: 1 → 18 days *(between Dx& 1st treatment)*	≤ 9 days *(betweenDx&T1)*
3.ii: *< 20% subjects missed on the basis of time-related constraints (ie. start of treatment or lab availability)*	NR	< 20%
4. Test Performance & Tolerability		
4.i: Completion of all test components	93.9%	> 95%
4.ii: Incidence of AE &AC	0.67% AE & NR AC	< 1% AE &<10% AC
5. PCM Use *(cancer-related symptom management)*	NR	Reviewed post-study

Pt, Patients; AC, Active Complaints

Data Analysis

Severity of autonomic dysfunction was assessed using the CASS (Low, 1993b) using commonly measured indices of CV autonomic function (HR and BP). Spectral analysis of HR and BP variability both at rest and during head-up tilt (Novak, Novak, deMarchie, & Schondorf, 1995; Novak, Novak, & Schondorf, 1993; Schondorf, 1993) provided additional indices of the integrity of cardiac autonomic and sympathetic vasomotor innervation as well as a measure of baroreflex modulation of HR (Hughson, Quintin, Annat, Yamamoto, & Gharib, 1993; Schondorf, 1993). Other indices of baroreflex modulation were obtained from analysis of the cardiomotor response to the VM (Kautzner, Hartikainen, Camm, & Malik, 1996) and from the sequence method described by Blaber, Yamamoto, & Hughson (1995). T1 comparisons were made using standard t-tests. A 2x2 repeated measures ANOVA was performed on all self-report and objective measures of ANS and CV function. Based on recent pilot study methodological recommendations, given the feasibility-nature of this investigation, a power analysis was not performed (Thabane et al., 2010).

Results

Subjects

Study recruitment took place from March 2010 to July 2011 (see **Figure 14** for summary). A total of fourteen cancer patients and thirteen sex-and age-matched controls were tested at T1. Subject demographic information is presented in **Tables 6** & **7** (data only provided for retained subjects completing both T1 and T2 assessments). The patient group consisted of a variety of diagnoses and stages of disease. Of these, twelve patients and eleven controls completed the second test. Study groups were closely matched in gender, age and body mass index (BMI). There was a significant difference

at T1 in weekly PA levels (MET•hrs•week^{-1}) between the patient (M=7.5 MET•hrs•week^{-1}, SD=7.6) and control (M=26.3 MET•hrs•week^{-1}, SD=22.9) groups; t(21)=2.594, p = 0.017. There was also a trend toward a significance difference in T1 BFI scores (patient (M=27.3, SD=14.2) and control (M=15.5, SD=13.2); t(21)=2.066, p = 0.051). No member of either group displayed evidence of severe ANS or CV dysfunction at either testing time point.

Table 6: Subject Characteristics (T1)

	Patient	Control
n	12	11
Sex (women)	67% (n=8)	55% (n=6)
Age (years)	35.0 ± 8.9	33.8 ± 8.1
Weight (kg)	66.5 ± 11.5	66.3 ± 12.5
BMI (kg•m^{-2})	23.0 ± 3.5	23.0 ± 2.1
BFI	27.3 ± 14.2	15.5 ± 13.2**
PA level, MET•hrs•week^{-1}	7.5 ± 7.6	26.3 ± 22.9 *
Predicted^* VO_{2max} L•min^{-1}	2.54 ± 0.70	3.29 ± 0.97**

* indicates significance ≤ 0.05
** indicates trend toward significance BFI p=0.051 & VO_2 p=0.058
^ used n=10 & 11 for analysis of patient and control groups, respectively

Table 7: Patient Demographics

Patient Diagnoses and Treatments:

Breast (n=5): 4 cycles FEC + Paclitaxel (n=1); 4 cycles AC (n=4)
Gastrointestinal
- ***Pancreatic*** *(n=1): Folforinox x 3 + Gemcitabine x 1*
- ***Colon*** *(n=1): Xelox x 4*
- ***Anal*** *(n=1): Mitomycin C + 5 FU x 4*

Hematological
- ***Hodgkin's Lymphoma*** *(n=2): ABVD*
- ***Non-Hodgkin's Lymphoma*** *(n=1): R-CHOP*

Other
- ***Adenocarcinoma (unknown origin)*** *(n=1): C-Pacli*
- ***Parotid (acinic cell carcinoma)*** *(n=1): C-Pacli*

Staging at Diagnosis (I-IV):

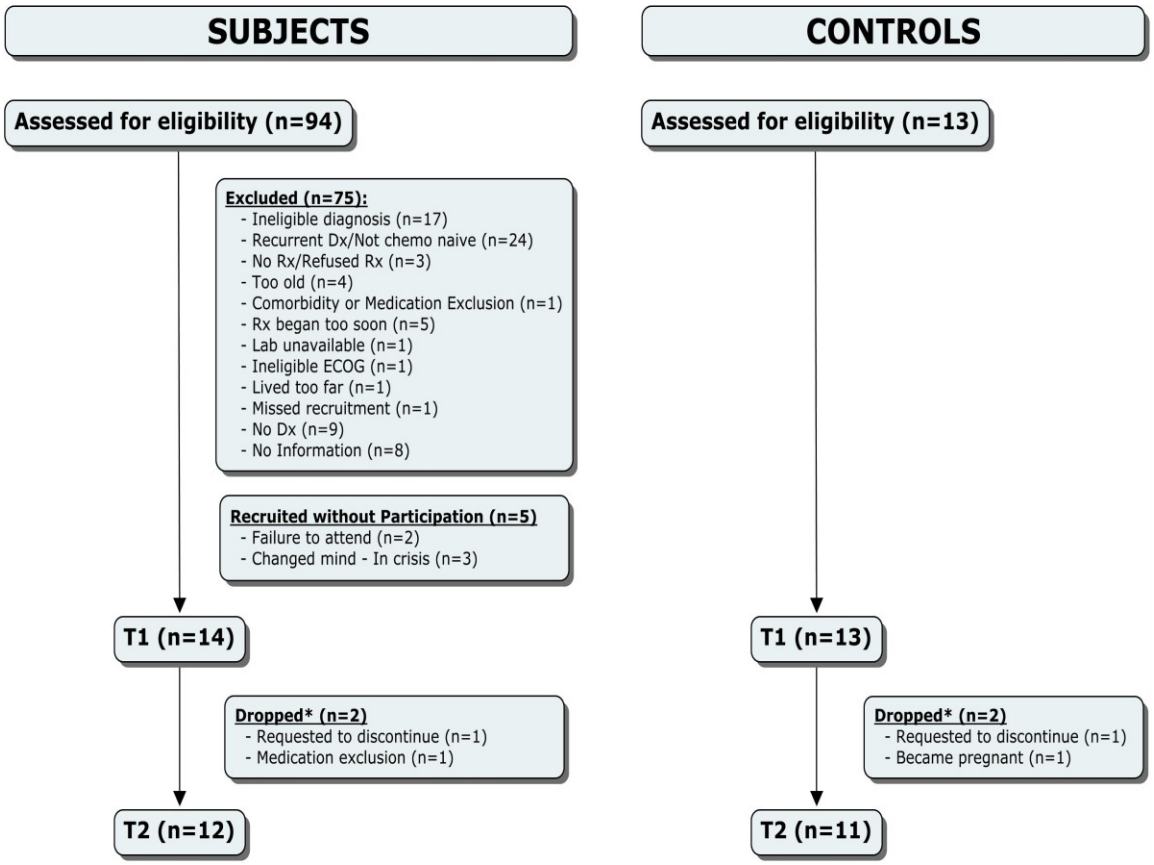
I – 1
II – 6
III – 3
IV – 3

Performance Status (0-4):

T1	T2
ECOG 0: 3	ECOG 0: 4
ECOG 1: 8	ECOG 1: 7
ECOG 2: 2	ECOG 2: 1

BMI:

T1	T2
23.3	23.5



* data not included in analysis

Figure 14: Subject recruitment

Feasibility Outcomes

We assessed the aforementioned feasibility concerns using the criteria in **Table 5**. In our opinion, and if successful, the achievement of these FC would suggest that the investigation of ANS function in cancer would be reproducible on a larger scale.

Criteria I: Patient Recruitment and Access (Table 8; Figures 15 and 16)

Over the course of the first 39 weeks of recruitment, due to stagnant recruitment rates, we amended our inclusion criteria three times to include recruitment from outside the AYA Oncology Program clinic, of patients having all tumour types (still excluding those directly involving the central and peripheral NSs and any effector organs of the CV system (heart, lungs, and vasculature)) and of patients up to 45 years (previously 39 years). As such, our recruitment reporting has been divided into two phases. Phase I includes the first 39 weeks of recruitment. Phase II includes the 26 subsequent weeks where no additional protocol amendments were made. Refer to **Figure 16** for an overview of patient diagnoses by recruitment phase.

Sub-Criteria I.i: Comorbidity and Medication Free

Of the twenty-eight otherwise eligible patients (OEP), only one person presented at T1 with previous CV or NS morbidity and use of related medication (*details: sinus arrhythmia, high BP and related medication use*). This accounts for a 3.6% incidence of the tested criteria, and therefore fits our established cut off of < 5%. Furthermore, and excluding the central and peripheral NS patients (n=16), the incidence of T1 CV comorbidity in all screened patients was 1 in 78 (1.3%).

Criteria 1: Recruitment & Access

Table 8: Patient Recruitment & Access

	Phase I *(05/03/10-10/12/10)*	Phase II *(11/12/10-12/06/11)*
TOTAL PATIENTS APPROACHED	**54 (57.5%** of total**)**	**40 (42.5%** of total**)**
TOTAL ELIGIBLE PATIENTS	**4** (7.4%)^	**23** (57.5%)
• *Successfully recruited*	**2** (3.7%)	**19** (82.6%)
TOTAL INELIGIBLE PATIENTS	**50** (92.6%)	**16** (40%)
• *Ineligible Dx*	**16** (29.6%)	**1** (6.3%)
• *Recurrent disease/not chemo-naïve*	**20** (37.0%)	**4** (25%)
• *No therapy/refuse therapy*	**1** (2.0%)	**2** (12.5%)
• *Age restricted*	**3** (6.0%)	**1** (6.3%)
• *No cancer/information*	**10** (20%)	**7** (43.8%)
• *ECOG > 2*	**0** (0.0%)	**1** (6.3%)
CRITERIA 1.i ***Comorbidity & Medication Free***	• < 5% exclusion based on T1 presence of CV/NS morbidity or use of PCMs	
FINDING	**FC 1.i was 100% achieved.**	
Total Eligible Patients Identified	**4** (7.4%)	**23** (57.5%)
• Weeks per phase	**39** (56.6%)	**26** (43.5%)
• Average weekly recruitment	**0.103**	**0.885**
CRITERIA 1.ii ***Patient identification***	• Successfully identify > 40 eligible patients per year	
FINDING	**FC 1.ii was 100% achieved.**	

Percentages reflect phase totals, unless otherwise stated.
^ based on eligibility criteria at the time

Sub-Criteria I.ii: Patient Identification (Figure 16)

Phase I subject identification was difficult, with only 7.4% of patients screened meeting our eligibility criteria (see **Figure 16** for summary of patient eligibility by phase). However, after having modified our inclusion criteria, Phase II patient identification rates were much better. Based on an identification average of 57.6% or 0.885 eligible patients/week, and extrapolating this 26-week experience over 52 weeks, our projected

identification rate was approximately 46 potential subjects/year. With our patient identification FC defined as ≥ 40 patients/year, and drawing from our Phase II experience, we feel that the projected identification rate of 46 patients/year lends itself to achieving adequate trial recruitment, especially if coupled with adequate infrastructure support. More specifically, due to the fact that the primary recruiter was also responsible for testing, the eventual testing volume increase likely caused some missed patient identification opportunities.

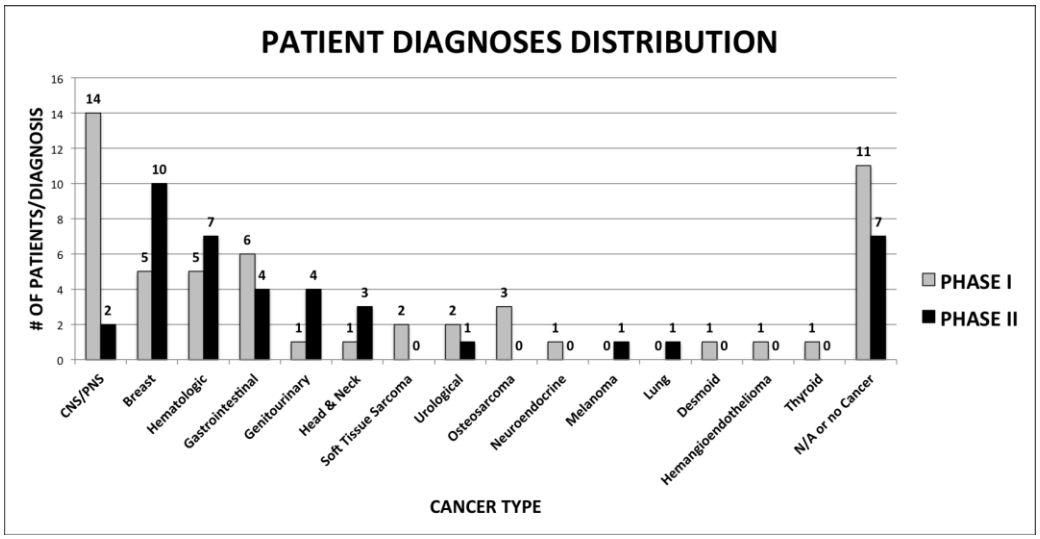


Figure 15: Overview of patient diagnoses by phase

Criteria 2: Subject Retention (Table 9)

We were successful in recruiting 19 patients for our study, with 14 completing T1. Three of the five untested patients initially agreed to participate but withdrew their consent once the reality of their Dx set in. Two from this group cited personal crisis and the third cited family crisis as their reasons for withdrawing consent. When followed-up with, the remaining two simply stated they had forgotten (at which point they had both begun treatment). The latter two incidence pointed out a methodological weakness in our recruitment approach, which was later corrected by implementing either email or

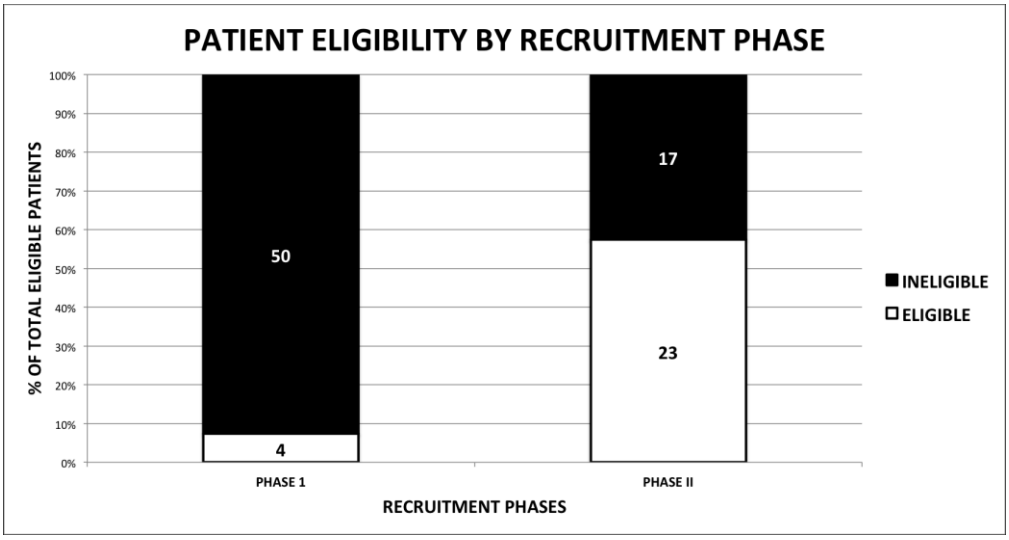


Figure 16: Patient eligibility by phase

telephone reminders the day before evaluations. During the routine phone booking of T2 assessments, one patient requested to discontinue participation. The reason for which was described as 'having too much on [their] plate' and nothing to do with the tolerability of the test battery. A second patient was dropped from study when we learned that they had an unreported previous history of cancer and related therapy (T1 data was dropped from analysis). In summary, of the 13 patients eligible to complete T2, 12 (92.3%) returned for testing; which fell just short of our FC of > 95% retention rate. It should be noted, however, that our retention rate of 92.3% was comparable to those reported in the literature of 91.8% (**Tables 4 and 5**).

Criteria 2: Retention

Table 9: Patient Retention Rates

	Subject Retention
T1 EVALUATION (T1)	
• Total recruited	**19** (70.1%)
• Completed T1	**14** (73.7%)
• Dropped from study *(failure to report previous use of potentially cardiotoxic therapy)*	**1** (5.3%)
• Patient discontinued	**1** (5.3%)
IN-TREATMENT EVALUATION (T2)	
• Total eligible for T2	**13** (68.4%)
• Total completed T2	**12** (63.2%)
• Retention rate	**92.3%**
CRITERIA 2 ***Patient Retention***	• > 95% retention rate (based on willingness and ability to participate and completion of T2 assessment)
FINDING	**FC #2 was 97.2% achieved.**

Criteria 3: Baseline Establishment (Table 10)

AYA Oncology Program clinic data indicated that, although 15.7% of new patients beginning treatment on the day of their first visit, there was a window of opportunity to collect our T1 measurements. According to these data, (Palumbo & Kavan, 2008) approximately 50% of patients began treatment within two weeks of Dx and an additional near 17% within a third week (not including the aforementioned 15.7%). Despite having upwards of 2-3 weeks to collect T1 data, considering the inevitable personal crisis following many cancer diagnoses, we were concerned that many AYAs may not prioritize participation. Further compromising our T1 collection capacity was the availability of the testing lab, whose primary function being clinical patient care.

Criteria 3: Pre-Chemo Baseline

Table 10: T1 Testing Opportunity

	T1 Testing Opportunity
Patient Recruitment Flow	
• Avg. # days between Dx& recruitment	**3.8**± 5.4
• Avg. # days between recruitment & T1 assessment	**5.3**± 4.4
• Avg. # days between Dx& T1 assessment	**9.1**± 6.2
CRITERIA 3.i	
T1 Testing Window	• ≤ 9 days between Dx and T1 evaluation
FINDING	**FC #3.i was 99.9% achieved.**
Time Related Exclusions	
• Total OEP	**26**
• # Recruited	**19**
• # treatment conflict	**5**
• # Investigator conflict	**2**
• Total time-related conflicts	**7**
CRITERIA 3.II	
Time-Related Conflicts	• < 20% subjects missed on the basis of time-related constraints (i.e. start of treatment, lab availability)
FINDING	**FC #3.ii was 91% achieved.**

Sub-Criteria 3.i: Days Between Dx and T1

McGill AYA Oncology Program data suggested that 67% of patients began treatment between 1 – 18 days following their Dx. Whenever necessary, we attempted to book all T1 assessments as quickly as possible. With an average of 9.1 days (SD=6.2) between Dx and T1, our results slightly exceeded our FC. However, two of our patients had > 6 weeks between initial Dx and commencement of treatment. As such, we did not expedite T1 testing of these patients. Had we, our reported average would have been lower.

Sub-Criteria 3.ii: Time-Related Testing Constraints

We sought to not miss recruitment of > 20% of OEP on the basis of time-related constraints. Of the 26 OEP, 19.2% of patients began treatment too soon to collect our T1 data. Despite making every effort to accommodate, an additional 7.7% of patients were lost to lack of lab availability. Overall, we had to exclude 26.9% of OEP on the basis of a time constraint, extending just beyond our 20% FC cut off.

Criteria 4: Test Performance and Tolerability (Table 11)

Sub-Criteria 4.i: Test Performance

At T1 evaluation, two patients presented moderately symptomatic (discomfort and pain related to tumour location). Without these symptoms, according to our eligibility criteria, the tumour locations would not have prevented testing. In each case, we decided to proceed with a modified testing protocol. At T1, Patient 1 completed all but the exercise component, and Patient 2 completed all but the VM and exercise components. At T2, Patient 1 (experiencing a prolapsing ostomy) and Patient 2 both completed all but the VM and exercise components.

Combining both trials for each group, the patient group completed 114 of 121 (94.3%) possible trials (including the two previously described patients); whereas, the control group completed 113 of 115 (98.3%) of possible trials. Comparing just the attempted trials in each group, only 2.6% of trials were stopped in the patient group vs. 1.7% of trials in the control group. Overall, with an established FC cut off of > 95% completion rate of all tests, the patient group average completion rate was (94.3%) and fell just shy of our criteria.

Sub-Criteria 4.ii: Testing Tolerance

This ANS test battery (Tilt, RSA, VM and QSART) has been used to test an array of patient groups (Low et al., 2004; Schondorf et al., 2000; Schondorf et al., 1999). Although we expected differences in performance outcomes, we did not anticipate differences in test ability or tolerance between groups. We assessed the testing tolerance by tracking the incidence of AC and AE. Standard of care in the delivery of these evaluations requires that evaluators 'check-in' with participants following each test. As such, general comments and complaints were regularly recorded. With respect to our criteria, AC was defined as a person voicing a concern about discomfort or evoked symptoms (without being prompted) or repeating previously expressed concerns beyond the initial check-in.

ACs were recorded in 6 of 117 (5.1%) attempted trials for the patient group and in 3 of 115 (2.6%) attempted trials in controls. There was 1 AE in 117 (0.85%) patient trials and no AE in controls. The AE took place during a T2 QSART test. In this case, the patient reported an unusually high level of discomfort during stimulation (recorded AC). When investigated further, the electrode used at that location appeared faulty. The lab supervisor was immediately called and cleared the patient to proceed with testing after assessing the mild skin irritation. Combining the incidence of the aforementioned factors (6 AC and 1 AE), overall evidence of testing intolerance was recorded in 5.1% of patient trials. In controls, intolerance was recorded in a total 3.5% of trials. Overall, we achieved our FC of < 1% incidence of AE (actual incidence 0.85%) and < 10% incidence of AC (actual incidence 5.1%).

Criteria 4: Autonomic and Cardiovascular Testing Capacity and Tolerability

Table 11: Patient Testing Performance and Tolerability

	Patients	Controls
Tilt Table		
• Total possible trials	25	23
• Total trials not attempted	0 (0.0%)	0 (0.0%)
• Total trials stopped	2 (8.0%)	2 (8.7%)
Self-Report Complaints & Comments		
• AC	2 (8.0%)	1 (4.4%)
• Passive Comments	1 (4.0%)	4 (17.4%)
RSA		
• Total trials completed	25	23
• Total trials not attempted	0 (0.0%)	0 (0.0%)
• Total trials stopped	0 (0.0%)	0 (0.0%)
Self-Report Complaints & Comments		
• AC	0 (0.0%)	0 (0.0%)
• Passive Comments	0 (0.0%)	0 (0.0%)
Valsalva		
• Total possible trials	25	23
• Total trials not attempted	2 (8.0%)	0 (0.0%)
• Total trials stopped	0 (0.0%)	0 (0.0%)
Self-Report Complaints & Comments		
• AC	1 (4.4%)	0 (0.0%)
• Passive Comments	0 (0.0%)	2 (8.7%)
QSART*(1x AE)*		
• Total possible trials	25	23
• Total trials not attempted	0 (0.0%)	0 (0.0%)
• Total trials stopped	0 (0.0%)	0 (0.0%)
Self-Report Complaints & Comments		
• AC	2 (8.0%)	1 (4.4%)
• Passive Comments	N/A*	N/A*
Astrand-Rhyming – Cycle Ergometer		
• Total possible trials	25	23
• Total trials not attempted	2 (8.0%)	0 (0.0%)
• Total trials stopped	1 (4.4%)	0 (0.0%)
Self-Report Complaints & Comments		
• AC	1 (4.4%)	1 (4.4%)
• Passive Comments	1 (4.4%)	0 (0.0%)

CRITERIA 4.i	
TEST PERFORMANCE	• *> 95% completion of all tests*
FINDING	**FC #4.i was 99.3% achieved.**

CRITERIA 4.ii	
TEST TOLERABILITY	• *< 1% incidence of AEs* • *< 10% incidence of AC*
FINDING	**FC #4.ii was 100% achieved.**

* virtually every subject (patient & control) mentioned varying degrees of discomfort
'Self-Report Complaints & Comments' percentages are calculated based on number of attempted trials.

Criteria 5: Potentially Confounding Medication Use (Figures 17 and 18)

The consideration and impact of common symptom management medication on physiologic patient outcomes has not been well reported in behavioural and clinical exercise cancer research. Even some of the most methodologically robust exercise intervention studies, assessing CV and functional outcomes during treatment, fail to mention the possible confounding influence of these medications (Courneya et al., 2008; Courneya et al., 2007; Courneya et al., 2009; Haykowsky, Mackey, Thompson, Jones, & Paterson, 2009; Mock et al., 2005; Mock et al., 2001; Pickett et al., 2002). Many patients undergoing chemotherapy are prescribed medications to alleviate pain, nausea, bowel irregularity, sleeplessness, depression, allergic reactions, boost blood cell counts and control inflammation. Given the possible CV and NS perturbations caused by these medications, it is surprising that their potential influence has been largely overlooked. After review of our patient medication use, we report the T1 incidence of potentially confounding medication (PCM) use in 2 of 13 patients (15.4%). Not surprisingly, T2 PCM use was reported in 10 of 12 patients (83.3%).

To mitigate the influence of PCM (and to allow optimal recovery from the previous treatment), to the best of our ability, we attempted to complete the T2 evaluation in the 3-6 days before the 5th cycle of chemotherapy. In doing so, we had hoped to avoid the confounding influence of PCM taken in support of the 4th cycle and in anticipation of the 5th. We were mostly successful in this effort with only 1 of 12 T2 patient evaluations (16.7%) taking place the day before treatment. Importantly, the use of these supportive medications is not easily predictable and depends on patients' symptom profile, treatment schedule and whether or not the symptom being managed is acutely related to therapy or a cancer-related life circumstance. Given our small sample size, we cannot suggest whether or not the use of PCM confounded our CASS results.

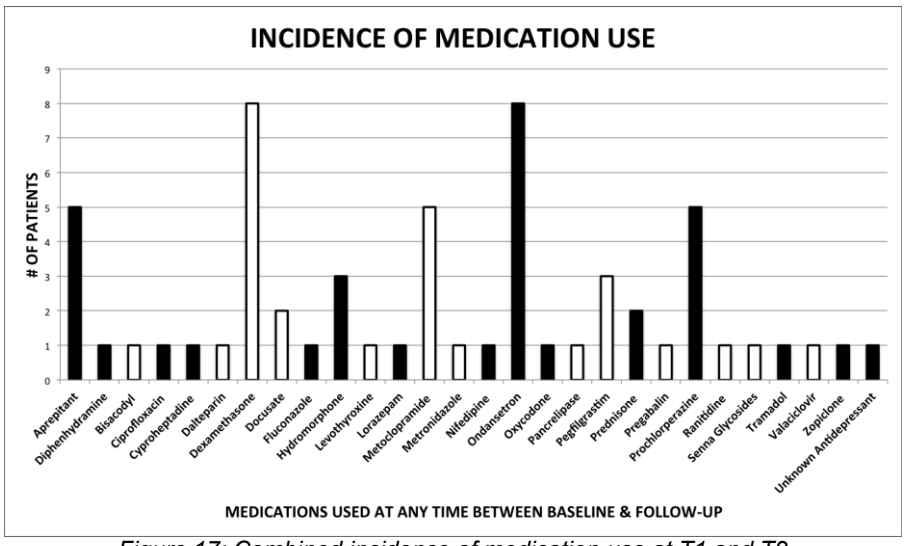


Figure 17: Combined incidence of medication use at T1 and T2

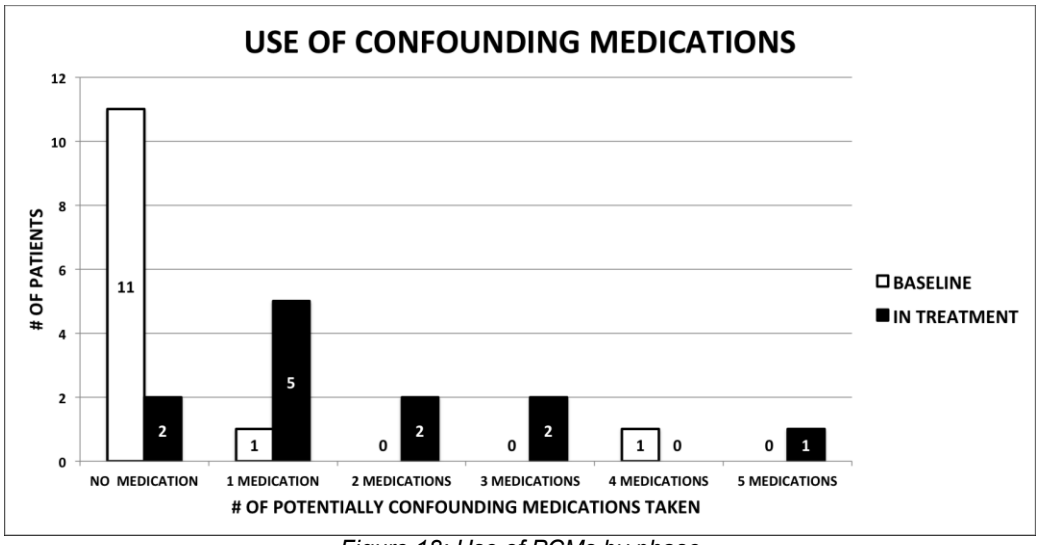


Figure 18: Use of PCMs by phase

Autonomic Testing: CASS

CASS Component Results

CASS component analysis revealed evidence of T1 cardiovagal impairment in 5/12 (41.7%) of our patients [moderate impairment: 3/12 (25.0%), mild impairment: 2/12 (16.7%)] compared to mild impairment in only 1/12 (8.3%) of our control group. QSART-evidence of sudomotor impairment was present at T1 in 4/13 (30.4%) of patients [severe

impairment: 2/13 (15.4%); moderate impairment 2/13 (15.4%)], compared to no evidence of impairment in the control group (see **Table 12**). No adrenergic dysfunction was evident at T1 in either group (see **Table 12**).

At T2, CASS component analysis revealed persistent cardiovagal impairment in 3/11 (27.3%) of patients [moderate impairment: 1/11 (9.1%); mild impairment 2/11 (18.2%)] compared to a consistent mild impairment in 1/11 (9.1%) control group members (see **Table 13**). T2 sudomotor assessment revealed persistent evidence of impairment in 5/11 (45.5%) patients [moderate impairment: 4/11 (36.4%); mild impairment: 1/11 (9.1%) (see **Table 12**). Again, no evidence of adrenergic impairment was detected (**Table 12**).

Preface: Results Interpretation (Figures 19-24)

In the following figures, the data points have been colour-coded within each group and according to subject. Circular data points reflect scores or measurements falling within normal age- and gender-related ranges. Whereas triangular and square data points reflect scores or measurements > 50% of lower limit and < 50% of lower limit, respectively, the normal age- and gender-related limits.

Table 12: CASS Component Scores

Sudomotor Function	T1				T2			
	# Tested	# Mild	# Moderate	# Severe	# Tested	# Mild	# Moderate	# Severe
Patients	13	0	2	2	12	1	4	0
Controls	12	0	0	0	11	0	1	0

Normative values taken from (Sletten, Weigand, & Low, 2010)

Cardiovagal Function	T1				T2			
	# Tested	# Mild	# Moderate	# Severe	# Tested	# Mild	# Moderate	# Severe
Patients	12	2	3	0	11	2	1	0
Controls	12	1	0	0	11	1	0	0

Normative values taken from (P. Novak, 2011b)

Adrenergic Function	T1				T2			
	# Tested	# Mild	# Moderate	# Severe	# Tested	# Mild	# Moderate	# Severe
Patient	11	0	0	0	12	0	0	0
Control	12	0	0	0	11	0	0	0

Normative values taken from (P. Novak, 2011b)

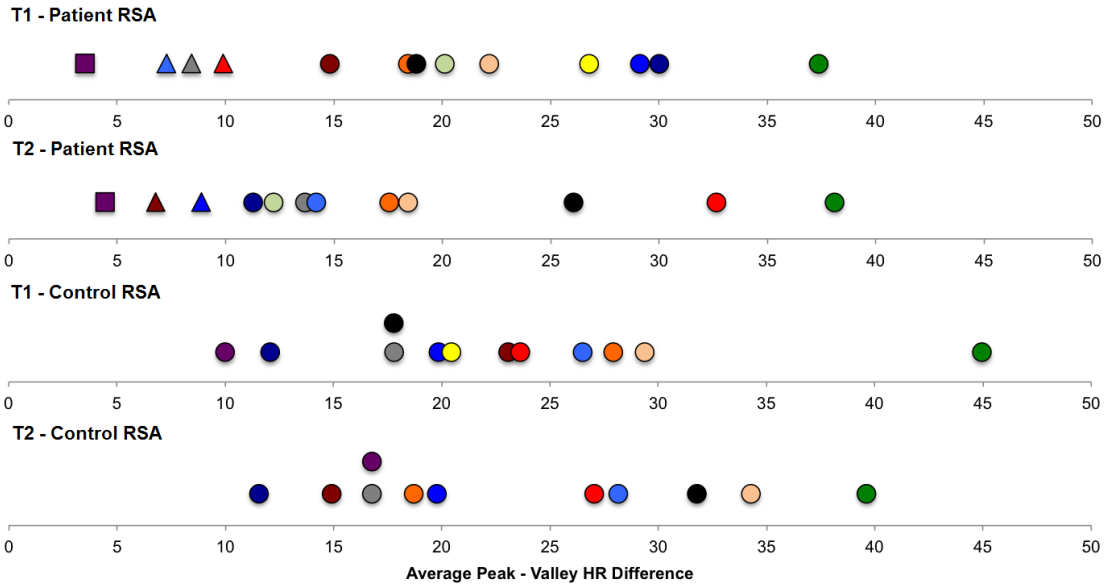


Figure 19: RSA results

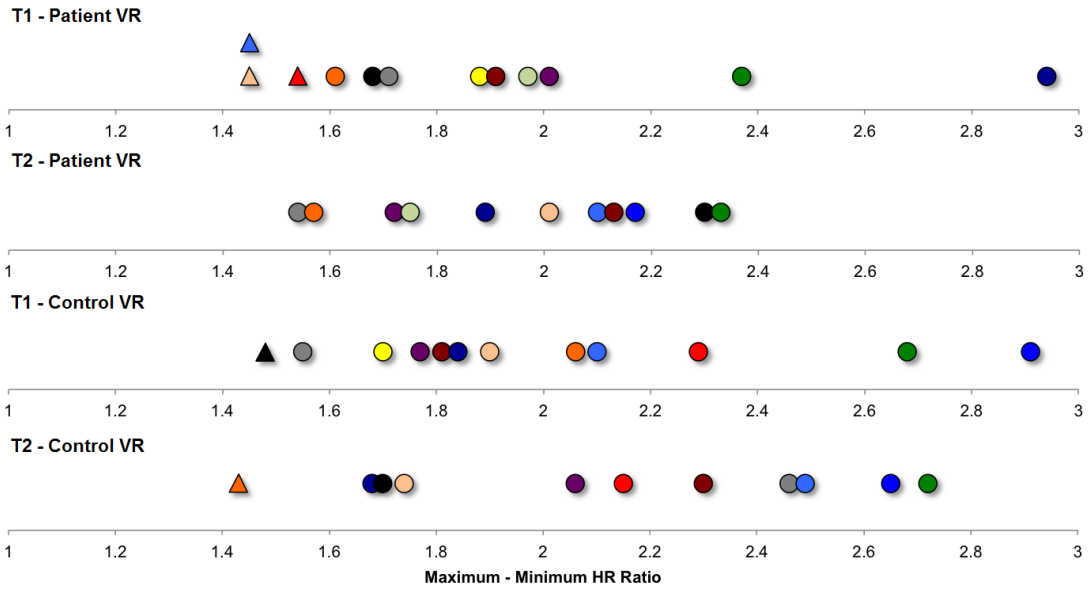


Figure 20: VR results

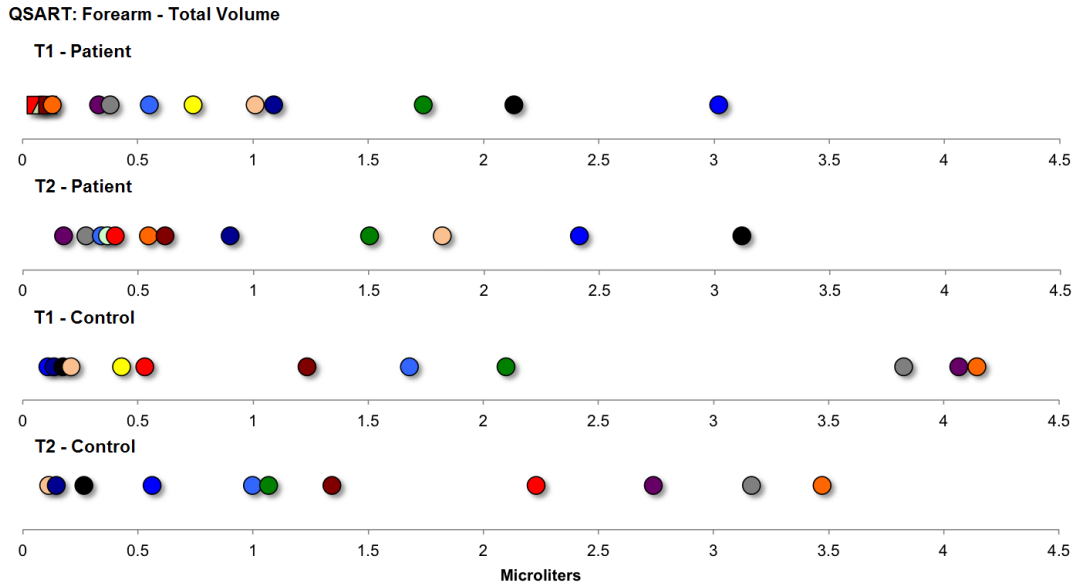


Figure 21: QSART results - Forearm

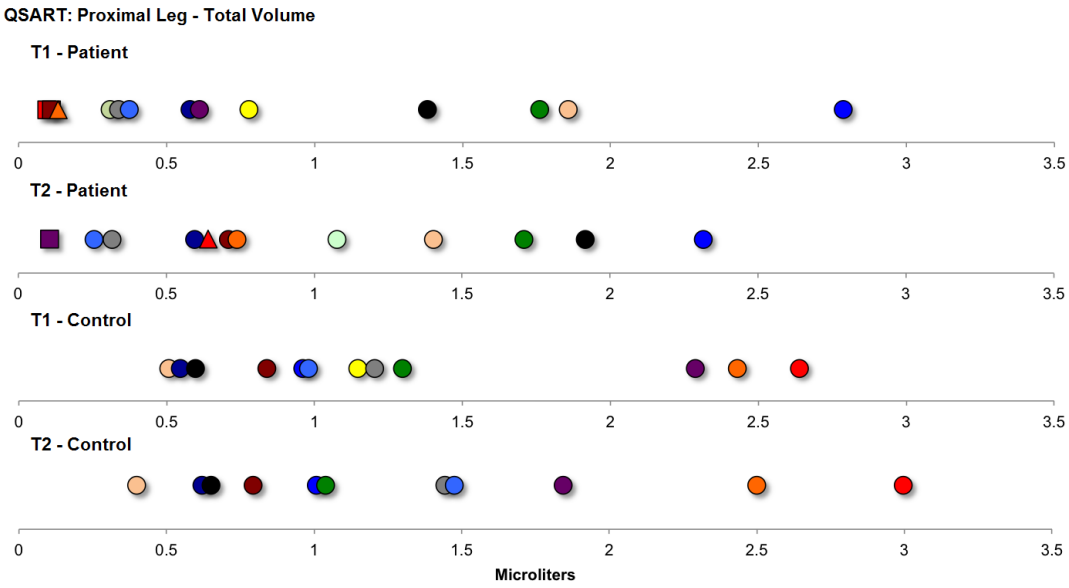


Figure 22: QSART results - Proximal leg

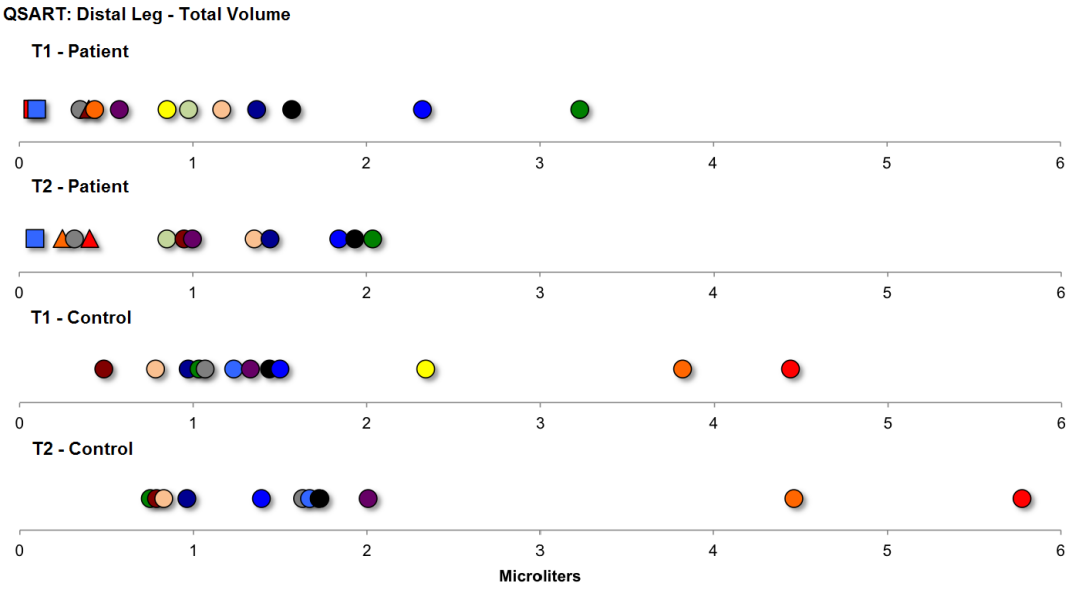


Figure 23: QSART results - Distal leg

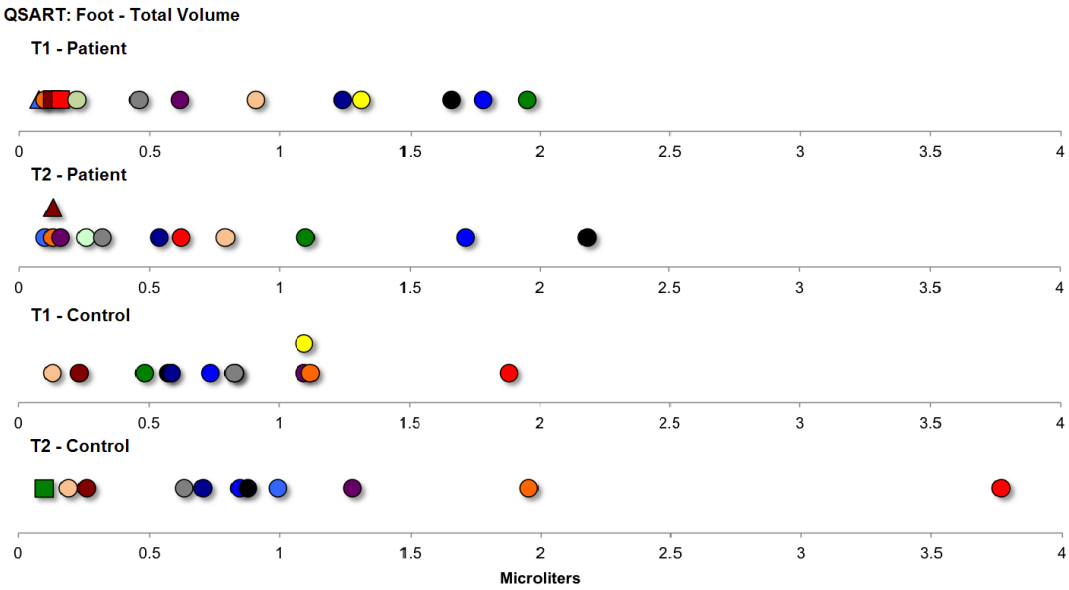


Figure 24: QSART results - Foot

Global CASS Results

Autonomic dysfunction is defined as a minimum score of two in any of the three CASS domains (cardiovagal, adrenergic and sudomotor), or a minimum score of one in at least two domains (Low et al., 2004). Using these criteria, our assessment of ANS function revealed the occurrence of mild or moderate ANS disturbances at T1 (38.5% vs. 0%) and T2 (33.3% vs. 9%) in patient and control groups, respectively (see **Figures 19-24** for raw and calculated ANS data, **Table 13** for total CASS scores). CASS comparison at T1 and T2 (**Table 13**) suggested a partial resolution of the patients' autonomic symptom profile (T1 CASS (M=1.39)(SD=1.71) vs. T2 CASS (M=1.08)(SD=1.38)).

Table 13: CASS Scores

CASS	T1			T2		
	Tested	Mild Neuropathy (2-4)	Moderate Neuropathy (5-7)	Tested	Mild Neuropathy (2-4)	Moderate Neuropathy (5-7)
Patient	13	4	1	12	4	0
Control	12	0	0	11	1	0

% Affected T1	**Patient 38.5%**	**Control 0%**
% Affected T2	**Patient 33.3%**	**Control 9%**

Exercise Testing: Modified Astrand-Rhyming Cycle Ergometer

At T1, predicted VO_{2max} performance appeared lower in the patient group (patient (M=2.54 ml $O_2 \bullet kg^{-1} \bullet min^{-1}$, SD=0.70) than in controls (M=3.29 ml $O_2 \bullet kg^{-1} \bullet min^{-1}$, SD=0.97); t(19)=2.022, p = 0.058), but the trend did not reach significance. At T2, predicted VO_{2max} was significantly different between patient (M=2.5 ml $O_2 \bullet kg^{-1} \bullet min^{-1}$), SD=0.66) and control (M=3.4 ml $O_2 \bullet kg^{-1} \bullet min^{-1}$, SD=0.95) groups; t(19)=2.559, p = 0.019. A 2x2 repeated measures ANOVA did not reveal any significant changes in measured (HR, BP and RPE) or calculated (HR & BP rates of change, absolute or relative VO_{2max}) endpoints between groups, across our two tests. There was, however, a significant effect of treatment on HR recovery [F(1,1) = 6.188, p = 0.027]. Similar to the direction of the CASS score trend, the HR recovery improved at T2.

Discussion

Feasibility of Autonomic Testing in Cancer

Through this feasibility study, we have endeavoured to establish recommendations and guidelines upon which future investigations of ANS function in cancer can be mounted. Overall, we averaged 98.2% success in achieving our FC. As

such, we are confident that a larger scale investigation of potential cancer-related autonomic dysfunction is possible. Despite this success, and drawing from our collective experience, we propose the following methodological considerations for those wishing to pursue related lines of research.

Methodological Considerations: Autonomic and Cardiovascular Testing in Cancer

1. Patient Recruitment, Access and Retention

a) Recruitment from a slightly expanded AYA age range (18-45 instead of 18-39) provided important recruitment opportunity and seemingly without exposing the sample to additional ANS or CV dysfunction and related use of medication.

b) To achieve an adequate sample size, without the staunch support of primary care staff (oncologists & nurses), requires either an omnipresent study recruiter or soliciting the assistance of key administrative hospital personnel. In our case, the team responsible for booking chemotherapy appointments was a tremendous help in identifying potential patients. Investigations targeting specific cancer populations should make every effort to verify the volume of appropriate patients before opening a trial. In our experience, given the absence of underlying comorbidity, screening for age and Dx are likely sufficient.

c) A cancer Dx is difficult at any age, AYA cancer being no exception. Despite the emotional onslaught following their Dx, AYAs appear highly motivated and capable of participating in studies of this nature. Bearing in mind that this was an observation trial, requiring an average of 3.5 hours for each of their two visits, we cannot generalize to the motivation and ability of AYAs to participate in intervention-based trials.

d) Additionally, at such a precarious time in life, the implementation of a reminder system (for pre-test protocol and appointment times) is likely an important component of AYA patient recruitment and retention.

2. Establishing a Pre-Chemotherapy Baseline

Using our clinical data, we had an idea of what our window of opportunity was to complete our T1 measures. Extrapolating from our own clinical/research experience and the literature, AYAs are at higher risk for being misdiagnosed or diagnosed late (Bleyer, 2002, 2007) for a variety of reasons. Regardless of the reason, the likely consequence of a late Dx is an advanced staging at Dx, and subsequently aggressive treatment of the disease. Although we cannot report actual incidence data, reason suggests that these factors work to narrow the available T1-testing window. Accordingly, it is imperative that investigators devise a means of identifying and booking patients for testing before the likelihood of PCM use increases. Given our moderate success (73.3% of OEP) in recruiting (M=3.8 days post Dx) and testing (M=9.1 days post Dx) patients from across multiple clinics, we suggest that investigators make every effort to not fall below our reported averages.

3. Test Performance and Tolerability

Consistent with our expectations, although not statistically powered, we report no difference in test tolerability between groups. That two members of our AYA patients group presented with symptoms that prevented the completion of the entire test battery is simply a reflection of their clinical reality. Comparison of all attempted trials suggests no clinically relevant difference in test performance or tolerance between patients and controls. We recommend proceeding with the test battery as described.

4. Potentially Confounding Medication Use

Again not statistically supported, we propose that, with the right planning, the influence of PCM on reported CV and NS patient outcomes may be minimized. Given the ease with which ANS function is perturbed, it is imperative that every effort is made to collect data within the period least likely to be influenced by PCM use. Supported by the partial resolution of ANS symptoms observed in our patient group at T2, we recommend that all in-treatment measures be collected within the 3-6 days prior to patients' subsequent treatments (assuming the average dose cycle for your study population is between 2-3 weeks per cycle). A window of least influence may be much more difficult to identify for treatment protocols involving weekly doses of chemotherapy or for patients taking PCM for chronic conditions/symptom management (i.e. antidepressants and sleep-aids). As such, it is extremely important that the future reporting of human observation and intervention trials include PCM data.

5. Varia

In an effort to better characterize the relationship between aerobic fitness and ANS function in cancer, future investigations should consider including basic standardized assessments of each. However, based on the apparent lack of sensitivity of the single stage Astrand-Rhyming protocol, submaximal incremental ramp or maximal exercise testing protocols may be more appropriate. Finally, investigators should account for and report any differences in aerobic fitness as it may influence or predict cardiovagal performance.

Autonomic Function in Cancer

Contrary to our hypotheses, as demonstrated by CASS, patient ANS function appeared slightly more impaired at T1 than T2. Similarly, aerobic performance (as

evidenced by a T2 improvement in HR recovery) appeared worse at T1. Although predicted VO_{2max} scores differed with greater significance at T2 (T1 (p=0.58) and T2 (p=0.019)).

The cardiovagal, adrenergic, and sudomotor CASS components reflect the integrity of parasympathetic, sympathetic, and sudomotor sympathetic branches of the ANS, respectively (Low, 1993b). Supporting the evidence for paraneoplastic-related autonomic dysfunction in cancer (Argyriou et al., 2005; Darnell & Posner, 2003; Nevruz et al., 2007; Turner et al., 1993; Viniegra et al., 1990; Walsh, Clark, Parhad, & Green, 1982), our T1 assessment revealed evidence of ANS impairment. Contrary to reports of increased ANS impairment during or following treatment (Argyriou et al., 2005; Viniegra et al., 1990), and similar to the findings of Turner et al. (1993), our results demonstrated persistent, yet partially resolved, ANS dysfunction in our patient group at T2. Importantly, there is evidence supporting the correlation between higher resting parasympathetic tone and higher aerobic fitness levels (Barney et al., 1988; Davy et al., 1996; De Meersman, 1992, 1993; Dixon, Kamath, McCartney, & Fallen, 1992; Goldsmith, Bigger, Steinman, & Fleiss, 1992b; Levy et al., 1998; Seals & Chase, 1989; Stein et al., 1999). Accordingly, interpretation of our T1 and T2 measures of cardiovagal function must include the potential confounding influence of the observed differences in aerobic fitness between our groups. Contrary to reports of chemotherapy-induced HRV attenuation (Fadul et al., 2010; Fagundes et al., 2011; Hirvonen et al., 1989), spectral analysis of the short-term HRV recordings (obtained during pre-tilt rest) did not reveal any observable fluctuation in parasympathetic activity, as indicated by the high-frequency domain. However, this was consistent with the findings of Ekholm et al. (2000), who suggested that the acute chemotherapy-induced changes may be more subtle and therefore not as easily detected using short-term (vs. 24-hour) recordings. Finally, to the best of our

knowledge, we are the first to report QSART evidence of sudomotor impairment in cancer.

Less clear is to what extent the observed ANS impairments will persist into survivorship and potentially impact the long-term quality of life of these patients. Related research has demonstrated persistent ANS impairment in cancer survivors, with and without advanced disease (Fadul et al., 2010; Fagundes et al., 2011; Hansen, 1990; Nuver et al., 2005; Strasser et al., 2006). If, in fact, cancer and anticancer therapy are responsible for causing long term ANS impairment or predisposing cancer survivors to related morbidity, the development of protective therapies is imperative. However, the reported testing methodologies of these studies varied in inclusion/exclusion criteria, ANS assessment techniques, as well as many did not control for known confounding comorbidities (i.e. diabetes and CVD) and related medications (i.e. various cardiac, antihypertensive and opioid use). Furthermore, in the absence of a pre-treatment baseline evaluation and the inclusion of a wide age-range of participants (19-79 years), it is difficult to assess whether the reported ANS impairments have resulted directly from the various cancers and anti-cancer therapies.

CV exercise training has been shown to preserve and improve markers of ANS and CV health in other populations (Rosenwinkel et al., 2001). However, dysfunction of either the parasympathetic, sympathetic or sudomotor ANS branches may uniquely compromise the ability of affected cancer patients to exercise. More specifically, the shift toward a “sympathetic dominant ANS balance,” caused by either vagal withdrawal or sympathetic hyperactivity, predisposes individuals to chronically higher resting metabolic rates (Rosenwinkel et al., 2001; Thayer & Lane, 2007), and therein an energetically unfavourable position. Furthermore, parasympathetic damage may hinder early exercise

adaptations to (Arai et al., 1989; Goldsmith, 1991; Robinson et al., 1966; Rowell, 1993), and recovery rates from (Imai et al., 1994; Ohuchi et al., 2000; Pierpont et al., 2000; Sears et al., 1998), exercise. Inadequate sympathetic adjustments are known to cause maladaptive BP responses (Low, 1997) and may limit the attainment of ME performance (Christensen & Brandsborg, 1973; Orizio et al., 1988; Robinson et al., 1966; Rowell, 1993). Finally, aberrant sweat responses, resulting from sudomotor dysfunction, may compromise thermoregulation and place exercising cancer patients at risk for heat injury (Bannister, Ardill, & Fentem, 1967) and related exercise intolerance.

Unfortunately, due to limitations in our study design, we were unable to provide evidence of any relationship between CV performance changes and the observed ANS dysfunction. Possible reasons for this include: i) insensitivity of the modified, single stage Astrand-Rhyming protocol, ii) small sample size and iii) wide range of normal biologic variability within our control group. Additional study limitations include: i) heterogeneity of diseases and related-treatments, ii) reliance on predicted, and not measured, VO_{2max} scores as indicators of aerobic fitness, iii) potential pre-test protocol violations, iv) inaccurate patient reported outcomes, v) the use of the BFI to compare across cancer and non-cancer populations and vi) unreported use of PCMs in our control group.

Acute and chronic autonomic impairment has been shown to have deleterious effects on quality of life and survival in health and a variety of disease states (Thayer & Lane, 2007). Initial evidence of cancer- and chemotherapy-related ANS dysfunction has been shown here and in the literature (in both the patient and survivorship settings) (Argyriou et al., 2005; Ekholm et al., 1997; Ekholm et al., 2000; Fadul et al., 2010; Fagundes et al., 2011; Hansen, 1990; Hirvonen et al., 1989; Hrushesky et al., 1991; Morrow, 2000; Morrow, Hickok, DuBeshter, & Lipshultz, 1999; Nevruz et al., 2007; Nuver

et al., 2005; Strasser et al., 2006; Turner et al., 1993; Viniegra et al., 1990; Walsh et al., 1982). However, without methodological consistency and standardization of assessment, accurate characterization of potential cancer- and chemotherapy-related autonomic damage is difficult. Considering the aforementioned methodological inconsistencies in previous ANS-cancer research, we had to rely upon methodologically robust, exercise oncology trials as the basis of our feasibility assessment. The utilization of exercise oncology trials as a foundation for our FC may be more relevant given the potential for using exercise as a modality to preserve and restore ANS and CV function in cancer, as has been described in other populations (Rosenwinkel et al., 2001). As such, future exercise intervention trials along related lines of research may need to be similarly structured.

Conclusion

The general aim of this study was to establish the feasibility of testing autonomic and CV function in AYA cancer patients undergoing treatment for cancer by: i) defining the methodological pitfalls and best-practice criteria for ANS testing in cancer, and ii) providing initial physiologic evidence of autonomic perturbations in cancer patients using the CASS. From a logistical standpoint, with a 98.5% average success rate in achieving the targeted FC, we are confident that future investigations of autonomic function in cancer are possible. However, given the multiplicity of confounding testing influences (i.e. lifestyle, age, comorbidity, cancer and the use of various anticancer therapies and supportive medications) the study of ANS function in cancer remains challenging. Cancer and chemotherapy are both known to impact effector organ function. As such, it may be necessary to conduct separate assessments effector organ function (i.e. multi

gated acquisition scans or pulmonary function tests) in an attempt to help localize cancer-related damage. Importantly, future investigations of autonomic and CV function, both during and following treatment, should make every effort to minimize the influence of PCM and to report PCM use whenever possible. Furthermore, to standardize the evaluation of ANS function in cancer, we strongly recommend the use of the CASS and components therein. Finally, contrary to our hypotheses, chemotherapy did not appear to significantly impair the autonomic responses to the CASS test battery. Although not statistically meaningful (due to small sample size), our main findings (diminished RSA and QSART) possibly suggest a common cholinergic mechanism of dysfunction. When considering the proposed mechanism of acetylcholine and vagal function inhibition of proinflammatory cytokine release (Tracey, 2002), it is interesting to speculate that if cancer-related parasympathetic dysfunction does exist, it may provide a pathway for CVD development in cancer patients.

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Appendix A

CALCULATIONS:

Incidence: approximately 10 000
5-year Survival: 72 men & 81 women
Average Life Expectancy: 79 men & 83 women

Between 1990-1999	*Men 20-44 (mean 32)*	*Women 20-44 (mean 32)*
Incidence	*38,339*	*62,035*
Survival	*27,840*	*48,506*
Mortality	*10,499*	*13,529*
Average life expectancy	*79*	*83*
Average years of life lost/impacted	*47*	*51*
Average years of life impacted	*47*	*51*
Total years of life lost	*493,453*	*689,979*
Total years of life impacted	*1,308,480*	*2,473,806*

SUMMARY:

- **Approximately > 350,000 years of life impacted (actual estimate 378,227)**
- **Approximately > 100,000 years of life lost (actual estimate 118,343)**

Appendix B

Cardiovascular toxicity of particular antineoplastic drugs.

Compound	Type of cardiovascular morbidity	Frequency of therapeutic use	Frequency of adverse effect
Anthracyclines and anthrachinolones			
Doxorubicin	CHF and LV dysfunction	+++	+++
Daunorubicin		+	+++
Epirubicin		++	++
Idarubicin		+	+++
Mitoxantrone		++	++
Alkylating agents			
Cyclophosphamide (high dose)	CHF	+	++
	Pericarditis/myocarditis		+
Ifosfamide	CHF	++	++
	Arrhythmias		++
Cisplatin	Hypertension	+++	++
	CHF		++
	Cardiac ischemia		+
Busulphan	Endomyocardial fibrosis	+	+
	Cardiac tamponade		+
Mitomycin C	CHF	++	++
Antimetabolites			
5-Fluorouracil	Cardiac ischemia	+++	++
Capecitabine		++	+
Cytarabine	Pericarditis	++	+
	CHF		+
Microtubule targeting agents			
Paclitaxel	Arrhythmias and conduction disorders	+++	++
	Hypotension		+
	CHF		+
Vinca alkaloids	Cardiac ischemia	++	++
Other cytotoxics			
Etoposide	Hypotension	++	++
Bleomycin	Pericarditis	++	+
Estramustine	Thrombo-embolic complications	+	++
Monoclonal antibodies			
Alemtuzumab	Hypotension	+	+++
	Hypertension		++
	CHF		+
Bevacizumab	Hypertension	++	+++
	CHF		++
	Thrombo-embolic complications		++
Cetuximab	Hypotension	+	+
Rituximab	Hypotension	++	++
	Hypertension		+
	Angioedema		++
	Arrhythmias		+
Trastuzumab	CHF and LV dysfunction	++	++
Tyrosine-kinase inhibitors			
Imatinib	Edema	++	++++
	Pericardial effusion		++
	CHF		+
Sorafenib	Hypertension	+	+++
	QT prolongation		++
	CHF and LV dysfunction		+
	Cardiac ischemia		+
Sunitinib	Hypertension	+	+++
	QT prolongation		++
	CHF and LV dysfunction		+±
Cytokines			
Interferon alpha	Hypotension	++	+++
	Cardiac ischemia		++
	Hypertension		++
	LV dysfunction		+
Interleukin-2	Hypotension	+	++++
	Arrhythmias		++
	Cardiac ischemia		+
Other drugs			
All-*trans*-retinoic acid	CHF	+	++
	Hypotension		++
	Pericardial effusion		+
Arsenic trioxide	QT prolongation	+	++++
Thalidomide	Edema	+	++
	Thrombo-embolic complications		++
	Bradycardia		++
	Hypotension		+

Legend: Frequency of therapeutic use: + – infrequent, for limited indications, ++ – moderate frequency of use, +++ – common use, for numerous indications; Frequency of adverse effect: + – rare, ++ – relatively unfrequent, +++ – frequent, ++++ – very frequent (due to difference in character, severity and clinical significance of particular toxicities it is impossible to assign uniform numerical values to these categories).

(Senkus & Jassem, 2011)

Appendix C

Overview of peripheral and central neurotoxic complications associated with various chemotherapy drugs

Drug	Neurotoxic complications		Management[a]
	CNS	peripheral nervous system	
Cisplatin	Rare: encephalopathy, headache, stroke, seizures	Sensory PNP with frequent off-therapy worsening, Lhermitte's sign, muscle cramps	Amifostine might protect in PNP
Carboplatin	Rare: cortical blindness	Sensory PNP	Caution with high doses
Oxaliplatin	No adverse effects	Postinfusion paresthesias, sensory PNP	Avoid cold drinks postinfusion; carbamazepine might ameliorate PNP
Vincristine	Overdose: encephalopathy, seizures, ataxia, athetosis, parkinsonism. Intrathecal: lethal radiculo-myeloencephalopathy	Sensorimotor PNP, mononeuropathy, cranial nerve palsy, autonomic neuropathy	Reduce dose intensity; glutamic acid, ganglio-sides and NGF may protect in PNP
Paclitaxel	Rare: acute encephalopathy, seizures	Sensorimotor PNP, myalgia, proximal muscle weakness	Reduce dose intensity; longer infusion time; amitriptyline for pain; NGF, glutamine, glutamate and amifostine may protect
Docetaxel	No adverse effects	Predominantly sensory PNP, Lhermitte's sign, proximal motor weakness	Dose reduction; pyridoxine for paresthesias
Methotrexate	Aseptic meningitis, transverse myelopathy, stroke-like syndrome, leukoencephalopathy, seizures	Lumbosacral radiculopathy	Caution with high doses; when possible, administer methotrexate before radiotherapy
Cytarabine	Aseptic meningitis, myelopathy. Rare: encephalopathy, seizures, and cerebellar dysfunction	Rare: painful sensory PNP, brachial plexopathy	
Fluorouracil	Rare: cerebellar dysfunction, inflammatory leukoencephalopathy	Rare: PNP	
Ifosfamide	Encephalopathy	Painful axonal PNP	Dose reduction; avoid use in combination with phenobarbital; methylene blue might reduce encephalopathy
Cyclophosphamide	Rare: blurred vision, confusion	No adverse effects	Dose reduction
Nitrosoureas	Rare: ocular toxicity, encephalopathy		
Procarbazine	Rare: drowsiness, stupor	Sensory PNP, ataxia, orthostatic hypotension, intrinsic hand muscle weakness	
Etoposide	Headache, seizures, somnolence	Sensory PNP	Dose reduction

a Thus far, neuroprotective agents are not widely used in everyday clinical practice; the agents mentioned in the table are studied *in vitro*, *in vivo* and in clinical trials.

NGF = nerve growth factor; **PNP** = peripheral neuropathy.

(Verstappen, Heimans, Hoekman, & Postma, 2003)