The Effects of Short-term High-Intensity Interval, Moderate-Intensity Continuous and Resistance Training on Cardiovascular Health in Older Adults

by

Myles W. O'Brien

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Abstract

Aging is associated with a decline in peripheral vascular endothelial function [i.e., flow-mediated dilation (FMD)] and cardiovagal baroreflex sensitivity (BRS), which are both critical to cardiovascular health. Accumulating evidence in younger adults suggest that high-intensity interval training (HIIT) provides superior benefits to cardiovascular health than moderate-intensity continuous training (MICT) and whole-body resistance training (RT). We tested whether 6-weeks of HIIT (n=6) improves upper- and lower-limb FMD and BRS more than MICT (n=9) and RT (n=8) in older adults (OA). FMD was assessed via high-resolution ultrasound. Cardiovagal BRS was assessed using Portapres® derived beat-by-beat systolic blood pressures and electrocardiogram-derived cardiac intervals via the 'spontaneous baroreflex sequence' method. Short-term HIIT and MICT elicited similar increases in BRS, brachial and popliteal FMD, whereas no changes were observed following RT. These results indicate that short-term aerobic training augments vascular health and blood pressure regulation more than RT in OA.

Keywords: flow-mediated dilation, exercise intensity, vascular aging, cardiovagal baroreflex sensitivity

List of Abbreviations Used

AAA = Acadia Active Aging

ADMA = asymmetric dimethylarginine

ANOVA = analysis of variance

BA = brachial artery

B-mode = brightness mode

BMI = body mass index

BRS = baroreflex sensitivity

Ca^{2+} = calcium

Ca^{2+}-ATPase pump = calcium-adenosine triphosphatase pump

5'GMP = 5 prime-guanosine monophosphate

cGMP = cyclic-guanosine monophosphate

CV = cardiovascular

DBP = diastolic blood pressure

ECG = electrocardiogram

eNOS = endothelial nitric oxide synthase

FMD = flow-mediated dilation

FVC = forearm vascular conductance

HIIT = high-intensity interval training

HR = heart rate

LVC = leg vascular conductance

MAP = mean arterial pressure

MICT = moderate-intensity continuous training

NMD = nitroglycerin-mediated dilation

NO = nitric oxide

NTS = nucleus of the solitary tract

1-RM = one-repetition maximum

PDE-5 = phosphodiesterase-type 5

POPA = popliteal artery

PP = pulse pressure

PPO = peak power output

Q = cardiac output

ROS = reactive oxygen species

RT = resistance training

SBP = systolic blood pressure

SR_{AUC} = shear rate area under the curve

SV = stroke volume

TPR = total peripheral resistance

TVC = total vascular conductance

VSM = vascular smooth muscle

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Chapter 1 – Introduction

In developed countries, heart disease and stroke are among the leading causes of death (158). Approximately 1.6 million Canadians are living with heart disease or have experienced a stroke (108). These high rates of cardiovascular disease contribute to an over-burdened healthcare system and costs in excess of $23 billion dollars per year in Canada (109). Older adults are at a greater risk of experiencing a cardiovascular event due to unfavorable age-related changes to their cardiovascular system (127). With increasing age comes an elevated risk of atherosclerosis due to alterations in arterial structural modelling, stiffness and a decline in endothelial function (16). Vascular endothelial dysfunction is characterized as a decreased ability to dilate in response to a physical or chemical stimuli and serves as a marker of cardiovascular disease risk (127). A reduction in the bioavailability of the endothelial-derived vasodilatory chemical nitric oxide (NO) is the primary mechanism mediating the impaired endothelial function in older adults (127).

Flow-mediated dilation (FMD) is a commonly used non-invasive technique that measures the bioactivity of endothelial-derived NO in peripheral arteries, and is most commonly assessed in the brachial artery (BA) (145). Although, BA-FMD serves as a predictor of future cardiovascular events (65), known heterogeneous responses exist between the BA and lower-limb vessels such as the popliteal artery (POPA) (150). Importantly, lower limb arteries are more susceptible to the development of atherosclerosis because of local hemodynamic factors and unique arterial wall properties (35), highlighting the importance of understanding how interventions designed to minimize age-related vascular dysfunction affect both the BA and POPA.

Regular aerobic exercise attenuates the age-associated deterioration in vascular function (149), with high-intensity interval training (HIIT) eliciting superior improvements in BA-FMD than moderate-intensity continuous training (MICT) (152, 159). These augmented HIIT-induced FMD responses may result from correspondingly higher increases in shear stress (i.e., the movement of blood over the endothelial cells responsible for stimulating NO production) than with MICT (147). Most previous reports that have compared vascular adaptations to these aerobic training protocols have been conducted solely in the BA of diseased populations with compromised vascular function (116). However, Rakobowchuk et al. (115) observed similar increases in POPA-FMD following both 6-weeks of sprint-interval training (i.e., repeated 30-sec Wingates) and MICT (65% of VO_2peak) in young (23.3 ± 2.8 years) healthy adults (115). Changes in POPA-FMD were not identified in a follow-up study by this group in sedentary young men, but they did report an increased BA-FMD response following six-weeks of MICT [45-min at 70% peak heart rate (HR)] (129). To date, there is a paucity of information regarding the effect that short-term aerobic training has on vascular adaptations in older adults, particularly in the lower-limb vasculature that are at a greater risk of developing peripheral vascular diseases (154).

It is recommended that older adults engage in resistance training (RT) a minimum of 2 days per week (26). To date, the effects of short-term RT on vascular endothelial function is understudied in this population (4). Resistance exercise elicits a larger post-contraction blood flow response than aerobic exercise at the same relative intensity (54, 81). However, this augmented blood flow response is transient and under high-pressure in comparison to the sustained low-pressure flow observed during aerobic exercise (39, 48,

147). It has been proposed that the shear stress response to RT may be too brief to result in vascular adaptations (114). As well, others have shown overperfusion occurs if blood-flow induced shear stress increases too much, which may result in tissue damage (144). Despite these differences in exercise-induced shear stress profiles, RT appears to be an effective stimulus for increasing BA-FMD in both young healthy (100, 114) and older people with a disease (73, 137). A meta-analysis by Ashor and colleagues (4) suggested that both aerobic and resistance training positively influence BA-FMD, with aerobic exercise leading to greater improvements (4). To date, the influence of RT-induced adaptations on the lower-limb vasculature of older adults remains unclear.

Arterial baroreceptors located within the aortic arch and carotid sinus rapidly regulate beat-by-beat changes in mean arterial pressure (MAP) (130). The arterial baroreflex has two separate efferent 'arms', the sympathetic baroreflex and the cardiovagal baroreflex, which mediate vasoconstrictor and heart rate (HR) responses, respectively (157). Cardiovagal baroreflex sensitivity (BRS) can be assessed by observing the relationship between HR (or cardiac intervals) to corresponding changes in systolic blood pressure (76). Cardiovagal BRS decreases with advancing age due to alterations in the neural and mechanical components (i.e., vascular stiffness within arteries containing the baroreceptors) of the arterial baroreflex contributing to a decreased ability to regulate blood pressure (64).

Regular aerobic exercise may attenuate the age-associated decline in cardiovagal BRS and partially restores the reduced BRS in previously sedentary middle- and older-aged individuals (91, 101). Madden et al. (86) demonstrated improved cardiovagal BRS in an older clinical population (i.e., with diabetes, hypertension and hypercholesteremic)

following 12-weeks of moderate-high intensity continuous training. Their protocol consisted of three, 1-hour sessions for 2 weeks at 50-60% HR_{max} and 80-85% of HR_{max} for the remaining 10-weeks. Pichot et al. (110) observed an increase in cardiovagal BRS in healthy elderly men following 14-weeks of cycling for 45 minutes at repeated bouts alternating between 65% HR_{max} (4-minutes) and 85% HR_{max} (1-minute). The improvements in BRS are likely due to the positive changes in aortic and carotid vascular compliance (i.e., barosensory vessels) and release of endothelial vasodilatory factors (e.g., NO) (68, 139).

Comparatively, the effects of RT on BRS are less clear, with studies demonstrating no change after 8 weeks of whole-body RT in young adults (30) or a *decrease* after 4-weeks of RT in middle aged adults (mean age: 47 years) (28). Conversely, cross-sectional work has demonstrated that middle-older aged (mean age: 50 years) rowers who engaged in frequent strength training had greater cardiovagal BRS in comparison to sedentary age-matched counterparts (29). Altogether, a paucity of research exists comparing the effects of different aerobic exercise training intensities or RT on cardiovagal BRS, with limited published data focusing on healthy geriatric populations.

The purpose of the present study is to investigate the effects of short-term (6-weeks) HIIT, MICT and RT on upper- and lower-limb conduit artery function and cardiovagal BRS in older adults. We hypothesized that HIIT would elicit superior improvements in BA-FMD, POPA-FMD and BRS than MICT. Additionally, we anticipated that both HIIT and MICT would enhance peripheral vascular endothelial function and BRS more than RT.

Chapter 2 –Review of Literature

2.1 – Overview of Cardiovascular Structure and Function

2.1.1 – The Cardiovascular System

The cardiovascular (CV) system is comprised of a pump and a vast network of vessels that are responsible for the transport of blood throughout the body. Specifically, the heart receives oxygenated blood from the pulmonary system, which is pumped throughout the body via larger arteries (131). These large arteries feed and branch into smaller arteries, arterioles and capillaries to exchange gases and nutrients to the organs (130). Once capillary exchange is complete, deoxygenated blood is transported back to the heart through the venules and subsequently the veins, where it is then pumped back to the lungs for re-oxygenation (131).

Arterioles may constrict or dilate as a means of controlling peripheral resistance and the effective distribution of arterial blood flow, such as to active muscle beds during exercise (130). The control of peripheral vascular resistance, in combination with cardiac output (i.e., the volume of blood delivered per minute), allows for effective regulation of mean arterial pressure (MAP) to ensure adequate delivery of oxygen and nutrients to the body (130).

2.1.2 – Peripheral Arteries

Arteries and arterioles are comprised of three distinct layers, as shown in Figure 2.1 (132). The outer layer, also referred to as the *tunica adventitia*, is composed of large amounts of collagen that protect and reinforce the blood vessel. The *tunica adventitia* contains sympathetic nerve endings, as well as, the vascular blood supply (i.e., the *vaso vasorum*). The middle layer (*tunica media*) is composed mostly of vascular smooth

muscle cells embedded in a matrix of collagen, elastin and glycoproteins, which are responsible for the maintenance of arterial lumen diameter and vascular tone (132). The innermost layer (*tunica intima*) consists of a single layer of endothelial cells, which serves as a selectively permeable membrane between the blood and underlying tissues (132).

As indicated above, the peripheral vasculature assists in the regulation of MAP by continuously contracting or relaxing as needed. Locally, the vascular tone, or degree of contraction is regulated by transmural pressure (i.e., pressure inside vessel – pressure outside vessel) via myogenic regulation (e.g., if the pressure inside the vessel increases, the vessel responds with a vasoconstrictor response) and chemical mediators produced in the endothelium that cause vasodilation (e.g., NO) and vasoconstriction (e.g., endothelin-1) (130). Extrinsically, vascular tone can be influenced by the medullary CV control centres (via sympathetic neural activity), hormones and the renin-angiotensin aldosterone system (130).

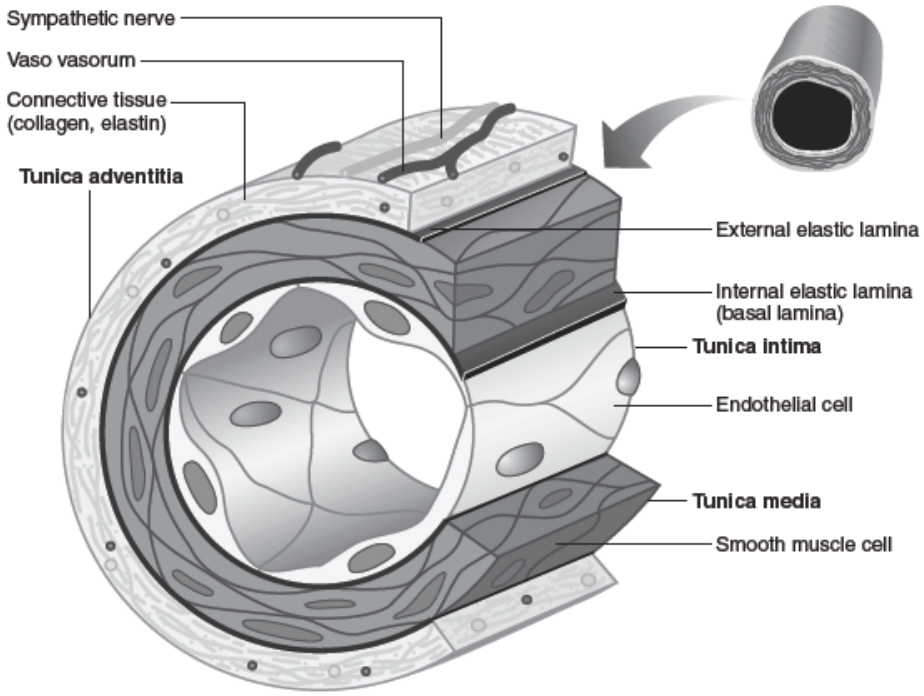

Figure 2.1: Cross-sectional representation of the layers of an artery (132). The tunica intima is comprised of a single layer of endothelial cells that are responsible releasing nitric oxide in response to an increase in blood flow-induced shear stress. The tunica media layer is composed mostly of vascular smooth muscle cells that vasodilate in response to endothelial-derived nitric oxide and exogenous provided vasodilators (e.g., nitroglycerin).

2.2 – The Arterial Endothelium

As mentioned above, the innermost layer of arteries and arterioles (i.e., *tunica intima*) is lined with vascular endothelial cells. In addition to regulating vascular tone, the endothelium may mediate the release of anticlotting and pro-clotting factors (25), defend against pathogens (132), control leukocyte movement in response to an inflammation and may initiate the formation of new blood vessels (23, 114).

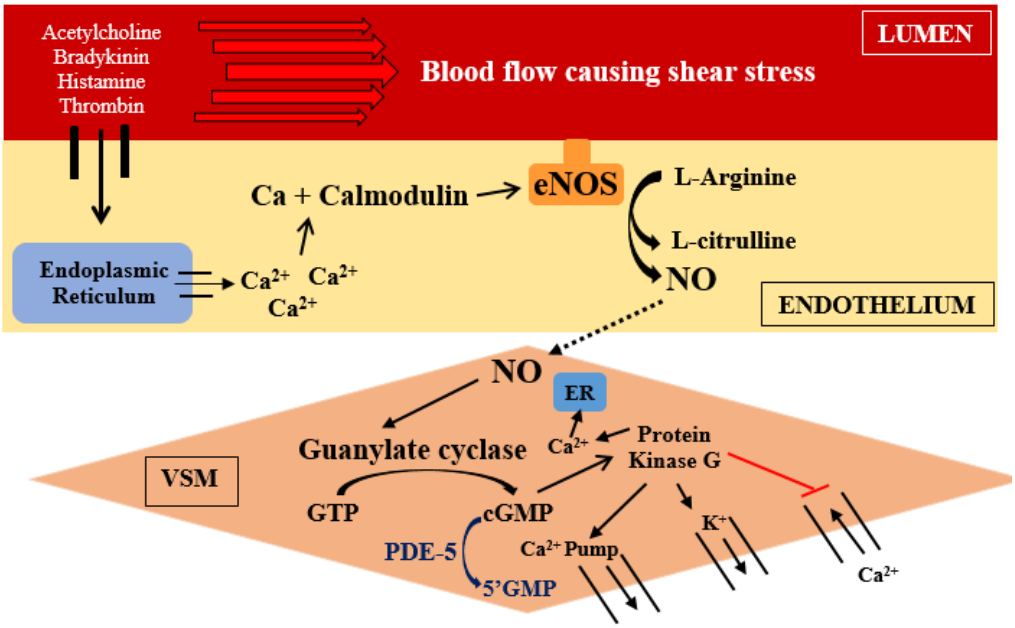

Figure 2.2: NO production and mechanism of action. Red line indicates the closing of L-type calcium channels (and thus calcium entry) via protein kinase G, which contributes to VSM relaxation. Blue reaction represents the degradation of cGMP to 5'GMP via PDE-5, which reduces the vasodilatory effects of cGMP. Ca^{2+}, calcium; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; VSM, vascular smooth muscle; GTP, guanosine triphosphate; cGMP, cyclic-guanosine monophosphate; ER, endoplasmic reticulum; K^{+}, potassium; PDE-5, phosphodiesterase-type 5; 5'GMP, 5-guanosine monophosphate; Ca^{2+}Pump, calcium-adenosine triphosphatase pump.

The production of NO by vascular endothelial cells is illustrated in Figure 2.2. With a rise in blood flow there is a corresponding increase in the frictional forces of the red blood cells against the lining of the lumen, otherwise known as shear stress (18). The anterograde (i.e., forward moving) shear stress is detected by cilia-like mechanoreceptors on the endothelium causing an increase in intracellular calcium and subsequently activating endothelial nitric oxide synthase (eNOS), which mediates the conversion of L-arginine to NO and L-citrulline (34, 46, 62). NO then rapidly diffuses into the surrounding VSM cells where it stimulates soluble guanylate cyclase and, increases cGMP concentrations. This leads to reductions in intracellular calcium levels resulting in VSM relaxation (132) (see Figure 2.2). Conversely, when VSM intracellular calcium

concentration increases, the ions bind with a calcium-modulated protein (Calmodulin). This calcium-Calmodulin complex then activates the enzyme myosin light-chain kinase (MLCK). MLCK phosphorylates the light chain on the myosin head that permits the myosin head to attach with actin, causing contraction of the VSM (i.e., vasoconstriction). As such, when intracellular VSM Ca^{2+} concentrations are reduced, myosin light-chain phosphatase removes the phosphate group from the myosin light chain causing the actin and myosin filaments to separate, resulting in VSM relaxation or vasodilation (132) (Figure 2.2.1).

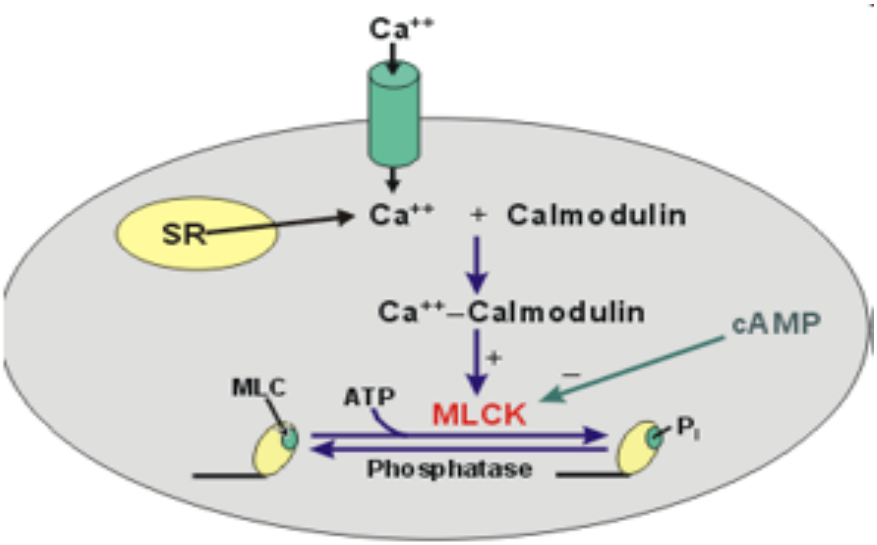

Figure 2.2.1: Contraction of the VSM with MLCK. An influx of Ca^{2+} into the VSM cell, through Ca^{2+} channels or from the SR, binds with calmodulin and activates MLCK. MLCK facilitates the binding of actin to myosin heads resulting in contraction of the VSM. Ca^{2+} reuptake into the SR reverses this process, and allows the VSM to relax. SR, sarcoplasmic reticulum; Ca^{++}, calcium; MLC, myosin light chain; ATP, adenosine triphosphate; MLCK, myosin light-chain kinase; cAMP, cyclic adenosine monophosphate; P_i, inorganic phosphate.

Although NO is a potent vasodilator, the endothelium also produces other important vasodilatory substances such as prostacyclin and endothelium-derived hyperpolarizing factor (132). Both prostacyclin and endothelium-derived hyperpolarizing

factor are activated when agonists (i.e., acetylcholine, bradykinin, substance P) bind to their respective receptors, contributing to VSM relaxation (84, 132). Additionally, the endothelium may release potent vasoconstrictors such as endothelin-1 in response to thrombin, interleukin factor-1, epinephrine, angiotensin II and vasopressin to assist in blood clotting and blood pressure regulation (84).

2.3 – Measures of Peripheral Vascular Function

2.3.1 – Flow-Mediated Dilation

Cardiovascular disease is initially characterized by endothelial dysfunction (40). The flow-mediated dilation (FMD) technique uses high-resolution ultrasound and is considered the gold standard non-invasive measure of NO bioavailability and endothelial function (56). Duplex ultrasound is recommended in order to simultaneously record artery diameter and blood flow velocity via brightness mode (B-mode) and pulsed-wave Doppler, respectively (161). To achieve this, a hand-held linear array transducer (i.e. probe) containing two arrays of piezoelectric crystals is placed on the surface of the skin to image the artery of interest. The piezoelectric crystals transmit pulsed signals to a specified depth and are reflected back to the transducer allowing the calculation of red blood cell velocity (i.e., blood flow velocity) (161).

As shown in Figure 2.3.1 below, B-mode imaging creates a two-dimensional image that allows the sonographer to view the anterior and posterior walls of the artery, and as such, the lumen diameter (i.e., dark band between the 2 cyan dotted lines). This recording is then played through customized automated edge-detection software (Cardiovascular Suite, Quipu), which is an objective and valid method of determining arterial diameter and FMD in a variety of populations (44, 52).

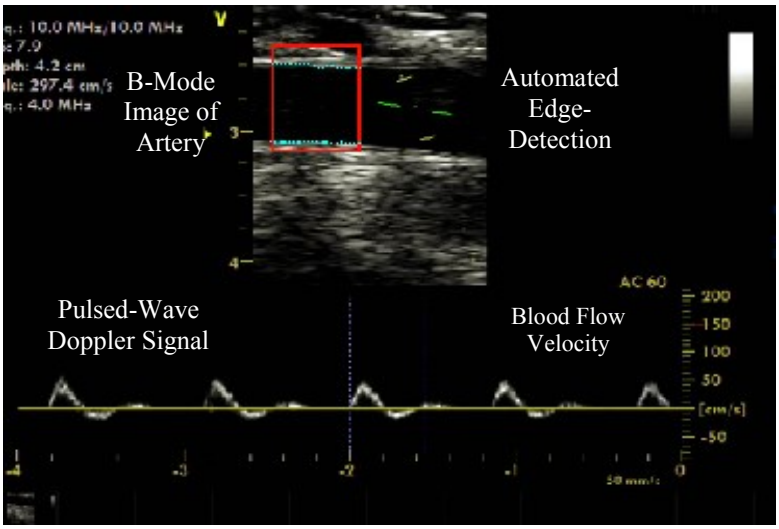

Figure 2.3.1: Example of the information observed from high-resolution duplex ultrasound imaging using both B-mode imaging and pulse-wave Doppler signals. B-mode, brightness mode.

The FMD technique, first proposed by Celermajer and colleagues (21) in 1992, is a surrogate measure of NO production (132). The FMD test initially consists of a baseline imaging period followed by a period of ischemia induced via a pressure-cuff inflated to a supra-systolic pressure located distal to the artery under investigation (145). Following, five-minutes of downstream ischemia, the cuff is rapidly deflated eliciting a large increase in blood flow, and associated shear stress (or frictional forces against the arterial walls). This triggers the release of NO from the endothelial cells and results in vasodilation (as shown in Figure 2.3.1.2).

FMD is typically represented as a percent dilation from the baseline diameter to the maximal diameter following the reactive hyperemia. Additionally, FMD is also normalized to the shear rate area under the curve (SR_{AUC}) between the time of distal cuff deflation until peak dilation occurs to account for inter-individual variations in the shear stress stimulus (103, 145).

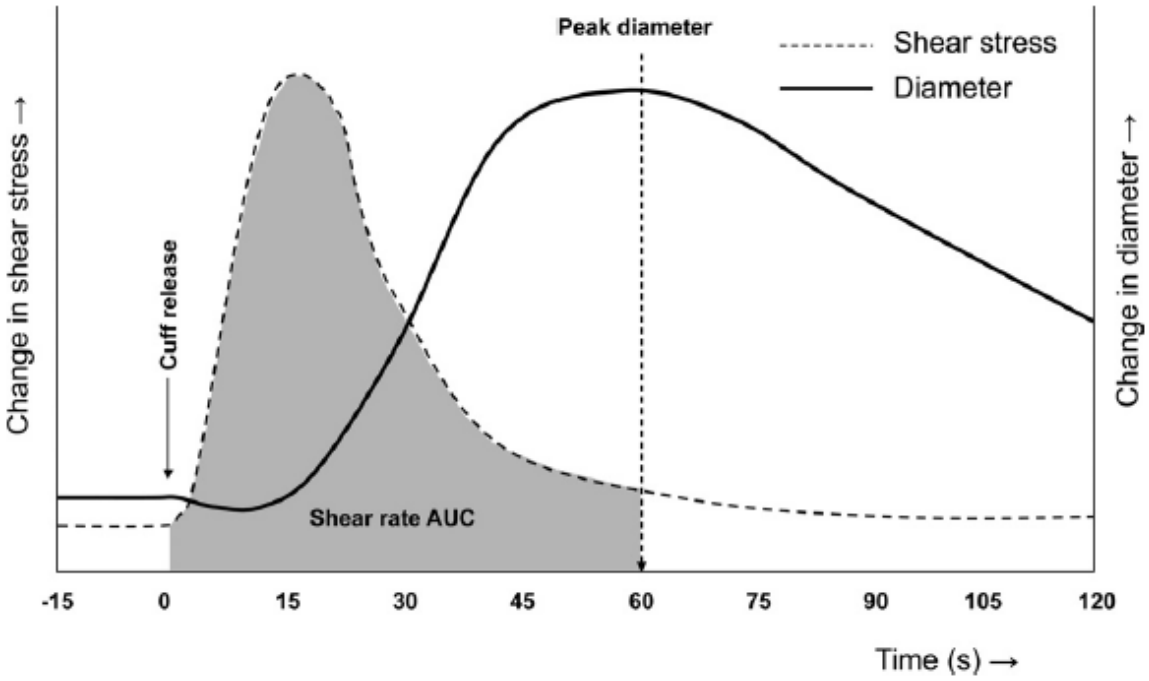

Figure 2.3.1.2: Normalizing FMD involves dividing the relative FMD response (i.e., the percent increase from the baseline diameter) by the shear rate area under the curve from the time of peripheral cuff deflation to the time that the peak increase in diameter is determined. AUC, area under the curve (145).

2.3.1.1 – Between-Limb Arterial Heterogeneity

Most studies incorporating FMD have been primarily performed in the brachial artery (BA) (145), which can provide predictive information regarding the incidence of future cardiovascular events (65). Known heterogeneous responses exist between the BA and lower-limb vessels, including the popliteal artery (POPA) (150). Such disparities in responses is due to artery diameter being inversely related to FMD, with larger arteries (e.g., POPA) dilating less than smaller arteries (e.g., BA) (146). Lower limb arteries are more susceptible to the development of atherosclerosis and peripheral vascular disease (35). The limb-specific differences in FMD may be attributed to the increased blood pressure in the lower limb due to greater gravity-induced hydrostatic pressures (97). Specifically, vessels exposed to elevated blood pressure have been reported to have a

decreased sensitivity (74, 82) and maximal responsiveness (50) to a variety of nitrovasodilators. With that, the lower-limb arteries supply a greater muscle mass and experience sustained increases in blood flow and blood pressure during locomotion, potentially altering the responsiveness of the POPA to a reactive hyperemia challenge (i.e., the FMD test) (160). Thijssen et al. (146) compared FMD in the brachial, radial, common femoral, superficial femoral and popliteal arteries and found that resting arterial diameter was inversely related to the peak FMD response. The BA has a much smaller lumen diameter than the POPA, and as such, experiences greater reactive hyperemia and subsequent vasodilatory response (150).

2.3.1.2 – Flow-Mediated Dilation in Older Adults

Increasing age is accompanied by structural and functional vascular adaptations. Structural modifications include greater arterial wall thickness, an increased wall-to-lumen ratio and less arterial elasticity (55, 95). Specifically, unfavorable changes in elastin and collagen that make up the arterial walls are observed in older persons, which in part, contribute to the decline in vascular function (121).

Accompanying the age-associated structural changes are chemical changes that attenuate FMD. At the endothelium, older adults have higher asymmetric dimethylarginine (ADMA) concentrations, which inhibit eNOS and the formation of NO (141). NO-induced vasodilation may also be inhibited by the overproduction of reactive oxygen species (ROS) that overwhelms the antioxidant defense systems, also referred to as oxidative stress (47). When ROS are produced in excess, superoxide (O_2^-) rapidly pairs with NO to form the highly reactive and highly toxic peroxynitrite (NO_3^-), reducing the bioavailability of NO (9). In general, older adults have exaggerated oxidative stress,

which is linked with cardiovascular disease and vascular dysfunction (10, 127). Evidence from animal models suggest VSM sensitivity may be decreased with age due to a decrease in soluble guanylyl cyclase activity, which produces cGMP and triggers VSM relaxation (Fig. 2.2) (23, 71). Lastly, older adults have exaggerated endothlin-1 and sympathetic nerve activity, which promote vasoconstriction and conversely, counteracts NO-mediated vasodilation (38, 98, 104).

BA-FMD progressively declines in men and women after the age of 40 and 50, respectively (20). While the temporal trends of POPA-FMD and aging are unclear, older adults have a markedly lower FMD response compared to their younger peers (107). Furthermore, older adults have an impaired reactive hyperemic response (i.e., SR_{AUC}), indicative of attenuated microvascular function (i.e., of the downstream arterioles) (15, 95). Of relevance, FMD normalized to SR_{AUC} is still marginally lower in older adults compared to younger adults (15, 107). This indicates that some of the negative vascular effects of ageing may not be solely related to attenuated endothelial-dependent vasodilatory mechanisms.

2.3.2 – Nitroglycerin-Mediated Dilation in Older Adults

Vascular health is not only dependent upon the function of the endothelium that lines the vessel, but also the function of the VSM that makes up the tunica-media (132). Endothelial-independent dilation (i.e., VSM sensitivity) may be assessed following the sublingual administration of nitroglycerin (24). Nitroglycerin is an NO donor, which activates soluble guanylate cyclase leading to vasodilation independent of endothelium-derived NO (134).

VSM reactivity to nitroglycerin declines with age in both the upper- and lower-limb arteries and resistance vessels (93). Specifically, Parker and colleagues (107) demonstrated that nitroglycerin-mediated dilation (NMD) was ~50% lower in older adults compared to young adults in both the BA and POPA. While the mechanisms behind the impaired NMD in older adults are unclear and understudied they may be due to decreased VSM expression of guanylyl cyclase, which is the main intracellular receptor of NO (71). As previously mentioned, aging is associated with increased inflammation and oxidative stress, which may reduce the bioconversion of nitroglycerin to NO within VSM cells (124), which may in part explain the decreased NMD in aged persons.

NMD is assessed using the same equipment as the FMD test. However, instead of a cuff-induced ischemia and resultant reactive hyperemia, a sublingual dose of nitroglycerin is administered and the artery of interest is imaged for 10-minutes afterwards (145). NMD is represented as a percent change in lumen diameter from baseline to peak dilation. Typically, short term exercise training studies (e.g., <12 weeks) have not observed changes in BA-NMD (4). However, exercise training-induced adaptations on POPA-NMD are less clear, especially in terms of arteries that supply the active muscle during lower-limb cycling exercise. As such, this study will only assess NMD in the popliteal artery.

2.4 – Cardiovascular Aging

There are a number of structural and functional changes in the heart with aging, which have significant implications for the development of cardiovascular disease. Structurally, older adults have increased in myocardial thickness as a result of increased

cardiomyocyte size compared to young adults (51, 102). As well, the heart changes in shape from an ellipsoid to spheroid with an asymmetric increase in the interventricular septum more than the free wall (61), which have important implications for cardiac wall stress and overall contractile efficiency. There are a number of functional changes and compensatory responses that the aged heart undergoes that diminish its ability to respond to an increased workload and decreases its reserve capacity. Specifically, there are unfavorable decreases in maximal heart rate, end-diastolic volume and contractility, and and increased end-systolic volume. As well, older adults have a prolonged systolic contraction and diastolic relaxation (138). These structural and functional changes of the heart reduce its pumping capacity, in particular the walls of the aorta become stiffer so that blood leaving the left ventricle experiences more resistance. Increased vascular resistance is associated with arterial stiffening and a linked incease in both arterial systolic pressure and pulse pressure (45).

With advancing age is an associated decline in arterial health, which is initially characterized by endothelial dysfunction or a decreased ability to dilate in response to physical or chemical stimuli (153). These age-associated physiological changes to vascular function increases the risk of cardiovascular disease (84). The mechanisms associated with aging-induced endothelial dysfunction is not fully known but there is evidence for functional and structural changes to the vasculature. With age, arterial remodelling occurs with increases in the arterial wall thickness and increases in the wall-to-lumen ratio (55). Additionally, arterial elasticity decreases with age due to reductions in the elastin and increases in collagen content of the arterial walls, which reduces vasodilatory capacity in response to various stimuli (121, 128). Older sedentary adults

also have exaggerated vasoconstriction due to an increase in sympathetic nerve activity and endothlin-1 production that contributes to the progression of arterial hypertension (153). Stiffer blood vessels and an imbalance of vasoconstriction versus vasodilation decrease the ability of the arterial baroreflex to regulate blood pressure and impair the arteries ability to vasodilate in response to a reactive hyperemia (127, 153). Arterial baroreceptors are mechanosensitive afferents that response to increases in vascular transmural pressure. Stiffer blood vessels have reduced distensibility and cannot stretch as far as healthy arteries, decreasing the sensitivity of the arterial baroreflex to respond to changes in blood pressure (89)

2.5 – Exercise Training on Vascular Function in Older Adults

One of the most important molecular consequences of regular physical activity and exercise is an enhanced NO bioavailability (123). Regular exercise enhances the synthesis and release of NO and attenuates the degradation of NO by free-radicals (53, 72). In general, a 10% increase in aerobic fitness results in a 1% improvement in relative BA-FMD (4). As identified in a recent meta-analysis (4), aerobic training ≥4 weeks typically increases the relative BA-FMD (%) of older adults by 2.9%. A 1% increase in relative FMD confers a 13% risk reduction in cardiovascular events (65).

The greater FMD observed in older adults who regularly perform aerobic exercise is mediated in part by enhanced NO bioavailability (142), which may be due to an increase in eNOS gene and protein expression (135). Other endothelial-derived vasodilators such as prostacyclin are also increased following aerobic exercise training, as observed in animal models (136). As hypothesized in a review by Seals and colleagues (126), the greater NO-mediated improvements in FMD following aerobic exercise

training in older adults may be secondary to the reduced oxidative stress. In older adults with disease, aerobic exercise training decreased the production of reactive oxygen species and expression of the oxidant producing enzymes [i.e., NAD(P)H oxidases] (1). Expression of the potent vasoconstrictor endothelin-1 in vascular endothelial cells also increases with sedentary aging (38). Aerobic exercise training abolishes the tonic endothelin (ET_A) receptor-mediated vasoconstriction observed in sedentary older adults (57). Altogether, the previous literature suggests endothelin-1 likely contributes to the decreased endothelial-dependent dilation in inactive older adults. In summary, regular exercise produces favorable modifications to the peripheral vasculature in older adults, who experience age-associated physical and chemical alterations that promote endothelial dysfunction (128).

2.5.1 – Aerobic Exercise Training Intensity on the Vasculature in Older Adults

While the benefits of aerobic exercise training on FMD are outlined above. Training at higher intensities may be a better stimulus for enhancing vascular endothelial function than moderate-intensity (i.e., 40-60% VO_2max) or light-intensity exercise (i.e., <40% VO_2peak) (116). It has been speculated that the superior benefits of high-intensity interval training (HIIT) over moderate-intensity continuous training (MICT) may be due to the greater exercise-induced blood flow response to the working skeletal muscles, which may promote more shear-stress induced NO formation (147, 159). With that, the increase in microvascular responses (or SR_{AUC}) following HIIT and MICT are relatively similar, suggesting there are other mechanisms likely responsible for the enhanced HIIT-induced vascular function beyond the current concept of increasing shear stimulus, potentially including reductions in oxidative stress and/or endothelin-1 (41, 116).

Most studies comparing HIIT and MICT in older persons have been conducted in individuals with disease, have exclusively assessed FMD in the BA, with training durations of 12+ weeks (32, 87, 88, 152, 159). However, adaptations in vascular endothelial function are believed to be greatest at earlier time points (i.e., 4-8 weeks) after which it then returns back to baseline and structural adaptation begin to occur, such as increases in lumen diameter (151). Conversely, the only other study to compare aerobic exercise training programs in older persons was 2 weeks in duration, which is believed to be too short of a time frame to observe BA-FMD improvements (70). Specifically, their exercise training protocol consisted of HIIT (10 × 60 second intervals at 100% peak power output interspersed with 60 seconds of passive recovery) versus MICT (40 minutes at 65% PPO). Additionally, Klonizakis et al. (70) only studied older women who had a relatively high baseline BA-FMD (8-9%), as such, a ceiling effect may have be present. In summary, while some research has compared the effects of exercise intensity on vascular adaptations, they have been primarily in the arteries supplying the non-active limb (i.e., BA) and have missed the postulated optimal "window" of functional improvements.

There is a paucity of information regarding the effects of short-term exercise training in the lower-limb vasculature that are at a greater risk of developing peripheral vascular disease (154). Rakobowchuk and colleagues (115) demonstrated six-weeks of sprint interval training [i.e., 4-6 repeated 30-second Wingates (0.075 kg/kg body mass) separated by 4.5 minutes of active recovery at 30 watts] and MICT (40-60 minutes at 65% of VO_2peak) similarly improved POPA-FMD in young adults. They failed to replicate these findings in a more recent study (129) that used a less intense sprint

protocol (i.e., 3 repeated 20 second Wingates) and a similar MICT protocol (i.e., 45 minutes at 70% HRpeak). However, they did observe an augmented BA-FMD response in the MICT group only. While these studies provide great insight into the role of exercise intensity in modifying the peripheral vasculature over the short-term (i.e., 6-weeks), the translation to older populations who experience age-related declines in FMD has not been investigated.

Some studies have postulated that an exercise intensity threshold may exist by which NO bioavailability may be jeopardized via high-intensity exercise-induced increases in ROS and a reduction in circulating antioxidants (11, 33). However, it is postulated that these potential detrimental effects may be avoided by limiting the time spent engaging high-intensity exercise by shortening the high-intensity intervals or introducing more frequent recovery periods between intervals, but specific recommendations are not provided (116). In addition to this, HIIT protocols incorporating shorter intervals (e.g., 15 seconds) at a higher intensity (e.g., 100 peak power output) with passive recovery have been shown to be most optimal for time spent at 80% VO_2max (i.e., stronger stimulus to improve aerobic fitness), perceived exertion and participant comfort among older adults than other HIIT protocols (58, 59). Herein, we used the information above to inform our proposed HIIT protocol, as described in more detail below.

2.5.2 – Resistance Training on the Vasculature in Older Adults

It is recommended that older adults engage in resistance training (RT) a minimum of 2 days per week (26). To date, the effects of short-term whole-body RT on vascular endothelial function is understudied in this population (4). Resistance exercise elicits a

larger post-contraction blood flow response than aerobic exercise (54, 81). However, this augmented blood flow response is transient and under high-pressure in comparison to the sustained low-pressure flow observed during aerobic exercise (39, 48, 147). If blood-flow induced shear stress increases too much, over perfusion could occur resulting in tissue damage (144). As well, it has been speculated that the RT blood flow response is too brief to result in arterial function adaptations (114). Despite these differences in exercise-induced shear stress profiles, overall, RT appears to be an effective stimulus for increasing BA-FMD in both young healthy adults (100, 114) and older adults with disease (73, 137, 155). A meta-analysis by Ashor and colleagues (4) suggested both aerobic and resistance training positively influence BA-FMD, with aerobic exercise leading to greater improvements.

Stensvold and colleagues (137) assessed BA-FMD in older patients with metabolic syndrome and demonstrated that a whole-body RT program using isokinetic RT machines and free-weights improved BA-FMD in 12 weeks. In an identical time-frame, Kwon et al. (73) observed a statistically significant 0.7±3.6% increase in BA-FMD following resistance band training in older women with type 2 diabetes. The RT program of the Vona et al. (155) study improved their BA-FMD (from 4.0±1.6% to 10.1±2.6%) in one-month of full body RT in older men and women with recent myocardial infarction. To our knowledge, no study to date has assessed the vascular benefits of short-term whole-body RT in healthy older adults and the influence of RT-induced adaptations on the lower-limb vasculature remains unclear.

2.6 – Baroreflex Function

As previously mentioned, MAP is a tightly regulated variable that ensures adequate blood flow to vital organs (130). MAP is the product of cardiac output (Q) and total peripheral resistance (TPR), which are both regulated by the arterial baroreflex. Specifically, mechanically-sensitive receptors located in the aortic arch and carotid sinus provide continuous feedback of MAP and pulse pressure (PP, systolic – diastolic blood pressure) (157). These high-pressure baroreceptors respond to changes in the pressure difference between the lumen and the outside of the vessel (i.e., transmural pressure) and send afferent signals to the medullary CV control centre (157). This area in the brainstem regulates the outflow of sympathetic (heart and blood vessels) and parasympathetic (heart only) neural activity (132).

The arterial baroreflex has two separate efferent 'arms', the first involved with sympathetic vasoconstrictor responses and the second that control changes in cardiac function (e.g. HR) (157). Cardiovagal baroreflex sensitivity (BRS) is determined by assessing the relationship between HR (or cardiac interval) to corresponding changes in systolic blood pressure (76). Whereas the sympathetic vasoconstrictor arm of the arterial baroreflex can be determined via the relationship between diastolic blood pressure (DBP) and vasoconstrictor sympathetic nerve activity (157). Since sympathetic activity will not be collected in this present study, we will be focusing on the cardiovagal BRS.

Upon an increase in MAP and associated increase in arterial stretch, baroreceptors send more afferent neural information to the medullary CV centre where the action potentials synapse on the nucleus of the solitary tract (NTS) (157). The cardiovagal baroreflex is then mediated via the NTS through innervation to the nucleus ambiguus and

dorsal motor nucleus of the vagus, which inhibit the sinoatrial node to lower both HR and MAP (via the corresponding reduction in cardiac output) (157). These responses are opposite during a transient decrease in MAP.

2.6.1 – Assessment of Cardiovagal Baroreflex Sensitivity

Human cardiovagal BRS may be assessed through intravenous injections of vasoconstrictor (e.g., phenylephrine) and vasodilator (e.g., nitroprusside, nitroglycerin) drugs that increase and decrease MAP, respectively (42). The Oxford technique involves analyzing beat-by-beat changes in SBP and cardiac interval following injection of phenylephrine, whereas, the modified Oxford involves the injection of the vasodilator nitroprusside before phenylephrine (22, 42, 106).

Another method of assessing cardiovagal BRS involves the Valsalva maneuver, consisting of a forced expiration against a closed glottis or elevated airway pressure for 15-20 seconds followed by a resumption of normal breathing (133). The forced expiration increases intrathoracic and intra-abdominal pressures that decrease venous return, stroke volume, cardiac output and MAP. Upon resumption of normal breathing there is a transient fall in MAP, followed by a baroreflex-mediated rebound in blood pressure and increase in HR (22). Baroreflex control of HR may be quantified as the ratio of the maximum to minimum HR during the maneuver (i.e., Valsalva Ratio) (106, 133). The slope of the SBP-HR relationship following re-breathing may also be utilized as an index of cardiovagal BRS (133).

Neck suction (i.e., simulated hypertension) or neck pressure (i.e., simulated hypotension) via an external neck chamber device evokes carotid baroreceptor-mediated CV responses by changing the transmural pressure across the carotid sinus wall (43). The

magnitude of neck pressure or suction may be altered to apply multiple, step changes in carotid transmural pressure permitting the assessment of the carotid cardiovagal BRS and construction of a sigmoidal baroreflex function curve (22, 43).

The aforementioned assessments methods of cardiovagal BRS in humans require invasive laboratory procedures (e.g., arterial catheters for vasoactive drug administration) and/or specialized laboratory equipment (e.g., neck pressure chamber). Computer-based analysis of normal fluctuations in resting systolic pressure and cardiac intervals (or HR) enables the calculation of spontaneous BRS. Two general methods are used to calculate spontaneous BRS, which are the spectral method and the sequence technique (106). The spectral method utilizes spectral analysis to analyze oscillations in blood pressure and HR in the low-frequency (0.1 Hz) and high-frequency (>0.15 Hz) ranges (105). BRS is estimated via the square root of the ratio between the cardiac intervals and systolic pressure spectral powers with the low-frequency and/or the high-frequency bands (105, 106).

As will be employed in this study, the sequence method involves the detection of 4 or more consecutive heartbeats where SBP and cardiac interval change in the same direction (13, 106). Sequences in which both variables increase are referred to as “up” sequences and conversely, “down” sequences when they both decrease. The average slope of the linear systolic pressure – cardiac interval index relations for all baroreflex sequences provides an estimation of BRS (see Figure 2.1.5) (22).

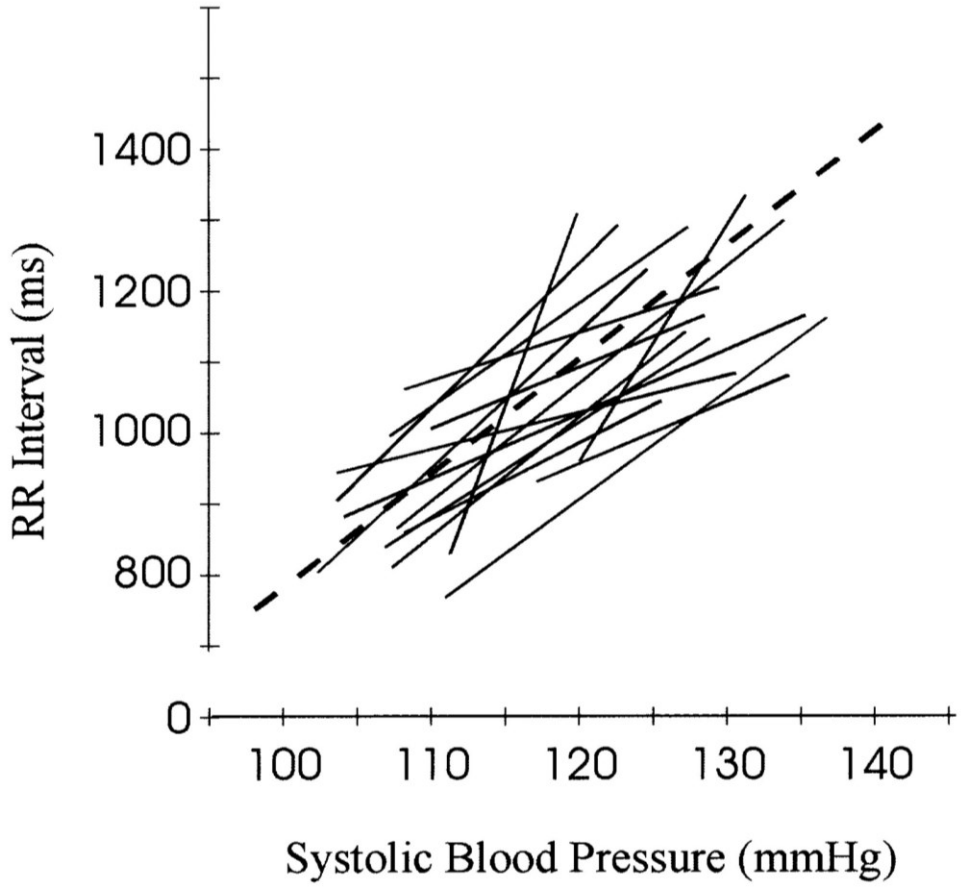

Figure 2.6.1: Example of baroreflex sensitivity calculation by sequence method of a single participant. Each solid line represents a regression slope of a sequence in which RR Interval (i.e., cardiac interval) and SBP concurrently increased or decreased for 4 consecutive heartbeats. The dotted line represents the average regression for all 'up' and 'down' sequences and provides an index of cardiovagal baroreflex sensitivity (112).

2.6.2 – Cardiovagal Baroreflex in Older Adults

Cardiovagal BRS is inversely and linearly correlated with age (r = –0.65-0.69) (75, 90). The age-related decline in cardiovagal BRS may be attributed to arterial stiffening within barosensory containing segments of the carotid artery and aorta, based on the observations that arterial stretch is a key determinant of baroreflex activation and aging decreases arterial compliance (2, 8, 36). Additionally, there are human data to

suggest decreased muscarinic M_2 receptor density on the sinoatrial node of the heart (17), reduced cardiac responsiveness to muscarinic receptor activation (113), and attenuated pre-junctional modulation of acetylcholine release in the atria that occurs with aging (99). Any of these factors may be responsible for the impaired BRS observed in older adults. Early cross-sectional work demonstrated that both vascular (i.e., mechanical transduction of pressure into barosensory vessel stretch; carotid stiffening) and central neural deficits (i.e., neural transduction of baroreceptor stretch into vagal outflow) were responsible for the decline in BRS in older adults, and that long-term physical activity attenuated these deficits (64). In a more recent study, it was demonstrated that the exercise-induced improvements in BRS were attributed more so to the neural component of the arterial baroreflex but positive changes in the mechanical component were also observed but not related to the magnitude of the exercise stimulus (36). Furthermore, intravenous infusions of ascorbic acid augmented cardiovagal BRS in older adults, which suggests that oxidative stress may contribute to the age-associated reduction in BRS (92). Furthermore, the decreased oxidative stress may result in an attenuated breakdown of NO by free radicals, resulting in an enhanced transmission of afferent signals through the NTS and a more sensitive arterial baroreflex (143).

2.6.3 – Aerobic Exercise Training on the Cardiovagal Baroreflex in Older Adults

Regular aerobic exercise may attenuate the age-associated decline in cardiovagal BRS and partially restore the loss of BRS in previously sedentary middle- and older-aged individuals (91, 101). Madden et al. (86) demonstrated an improved cardiovagal BRS in an older clinical population (i.e., with diabetes, hypertension and hypercholesteremic) following 12-weeks of moderate-high intensity continuous training consisting of three, 1-

hour sessions for 2 weeks at 50-60% HR_{max} and 80-85% of HR_{max} for the remaining 10-weeks. Pichot et al. (110) observed an increase in cardiovagal BRS in healthy elderly men following 14-weeks of cycling for 45 minutes at repeated bouts alternating between 65% HR_{max} (4-minutes) and 85% HR_{max} (1-minute). The improvements in BRS may due to the positive changes in aortic and carotid vascular compliance (i.e., barosensory vessels) and release of endothelial vasodilatory factors (e.g., NO) (68, 139). With that, 8 weeks of MICT (70% HR_{max}) has been shown to improve carotid artery compliance in older adults. However, this same positive effect was not observed following HIIT consisting of (4×4 minutes at 90% HR_{max} interspersed with 3×3 minutes of active recovery at 70% of HR_{max}) (69).

A paucity of research exists comparing the effects of different aerobic exercise training intensities on cardiovagal BRS, with studies focusing on geriatric populations even more limited. One study compared 5 months of low-intensity (55% VO_2max) versus high-intensity (75% VO_2max) endurance exercise training in middle-aged adults (83). While neither group demonstrated significant improvements in BRS, a favorable trend was observed in the higher intensity group. The lack of difference may be due to their relatively fit sample (baseline VO_2max= ~40 ml/kg/min) (83). As such, more research is warranted to investigate the role of aerobic exercise training programs on modifying the age-associated decline in cardiovagal BRS.

2.6.4 – Resistance Training and Cardiovagal Baroreflex in Older Adults

It is recommended that older adults engage in RT a minimum of 2 days per week (26). To date, the effects of RT on cardiovagal BRS is understudied in this population. Recent meta-analyses demonstrate that short-term (i.e., 6-8 weeks) RT interventions have

little effect on central indices of arterial stiffness and produce minor, albeit some, improvements in endothelial function in older adults (3, 4). As previously mentioned, central arterial compliance and peripheral vascular function are known to influence cardiovagal BRS.

As reported by Cooke and Carter (30), BRS was unchanged following 8-weeks of whole body RT in young adults. However, Collier et al. (28) observed an adverse decrease in BRS following 4-weeks of RT in a sample of middle aged (mean age: 47 years) men and women. They also noted an increase in BRS following 4-weeks of aerobic training (30 minutes at 65% VO_2peak) (28). Cook et al. (29) compared cardiovagal BRS in healthy habitual rowers (mean age: 50 years) who engaged in regular RT and aerobic training to age-matched sedentary controls. The rowing group had a higher BRS, which was positively related to carotid arterial compliance (29). However, their exercise training consisted of *both* high-intensity aerobic and resistance exercise regimes. Altogether, the investigation into the independent roles of RT and aerobic training as means of altering arterial BRS in older adults is warranted.

2.7 – Research Question and Hypothesis

The purpose of this study was to investigate the effects of short-term (6-weeks) HIIT, MICT and RT on upper- and lower-limb conduit artery function and cardiovagal baroreflex sensitivity in older adults. We hypothesized that HIIT would elicit superior improvements in BA-FMD, POPA-FMD and cardiovagal BRS than MICT. Additionally, we anticipated that HIIT and MICT would enhance vascular endothelial function and arterial baroreflex sensitivity more than RT.

Chapter 3: Methods and Procedures

3.1 – Participants

Twenty-three older adults (16 females; age 56-83 years) were recruited from the Active Aging program at Acadia University (Table 1). Participants were cleared for moderate-vigorous physical activity using the physical activity readiness questionnaire plus (156). One participant in the HIIT group was taking Diuril, which is a diuretic used to lower blood pressure. One participant in each of the MICT and the RT groups were taking Synthroid, which is used to treat hypothyroidism. One person in the MICT group was asthmatic. One participant in the RT group was taking Coversyl Plus, which is both a angiotensin converting enzyme inhibitor and a diuretic and is used to lower blood pressure. During the study, participants were requested to continue taking all prescribed medications. To be eligible for the study, participants had to have a body mass index (BMI) < 40 kg/m^2, no physical limitations to exercise and a resting blood pressure < 140/90 mmHg. Participants were informed of the methods and study design verbally and in writing before providing written informed consent. They were then randomized to HIIT (n=6), MICT (n=9), or RT (n=8). All protocols and procedures conformed to the Declaration of Helsinki and were approved by the Dalhousie University Health Sciences (Appendix A) and Acadia University Research Ethics Boards.

3.2 – Experimental Design

Participants underwent four separate laboratory visits in total. Day 1 and Day 2 were conducted pre-training while Day 3 and Day 4 were completed following training. Days 1 and 3 involved measurements of height and body mass, which were followed by a graded, maximal cycling exercise test to determine aerobic fitness (VO_{2peak}). Peak power

output (PPO) was also recorded on Day 1 and used to establish exercise intensities for the two aerobic training protocols. Days 2 and 4 were dedicated to the assessments of BA and POPA vascular function. Due to scheduling, Day 2 was conducted either prior to, or a minimum of 48 hours (or maximum one-week) following Day 1 (i.e., graded maximal exercise test). To minimize confounding influences on endothelial-dependent dilation, vascular assessments were performed 6 hours post-prandial, and participants avoided strenuous physical activity, as well as, the consumption of products known to acutely influence FMD responses (e.g., caffeine, chocolate, kiwi, saturated fats, folic acid supplements, antioxidant and multivitamin supplements) for 24 hours, consistent with FMD guidelines (145). Participants replicated their diet prior to both the pre-training and post-training vascular measurements. All study visits were performed in a thermoneutral environment (21°C). To control for diurnal variations in blood pressure and vascular function, Visits 2 and 4 were performed at the same time of day (66).

3.3 – Experimental Protocols

3.3.1 – Anthropometrics and Peak Aerobic Fitness

Height and weight were measured using a calibrated stadiometer (Health-O-Meter, McCook Il, USA) to the nearest 0.5 cm and 0.1 kg, respectively. Waist circumference was measured from the uppermost lateral border of the iliac crest and recorded to the nearest 0.5 cm. An incremental and maximal exercise test on a cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands) was administered to determine VO_{2peak} via a mixing chamber-based commercial metabolic system (TrueOne 2400®, Parvomedics Inc., Sandy, UT). Following a 5-minute warm-up period of light-intensity cycling (30-50W), the workload was set at 1 watt per kilogram of body weight

and gradually increased by 15 watts every minute until voluntary exhaustion. Strong verbal encouragement was provided throughout the test. Upon completion of the test, the workload was immediately reduced to the warm-up level for a 5-minute cool-down period. The power of the last completed stage was considered as the peak power output (PPO, measured in watts). The primary criterion for the attainment of a VO_2peak was a plateau in VO_2 (change <2.1 ml/min/kg) despite an increase in workload. In the absence of a plateau, attainment of VO_2peak was based upon a respiratory exchange ratio of ≥1.10 or the inability to maintain the required pedal cadence (i.e., 60 revolutions per minute).

3.3.2 – Training Protocols

Training was conducted 3 times per week for 6 weeks. Warm-up and cool-down periods consisted of 5 minutes at 25% PPO for both the HIIT and MICT protocols. Cycling protocols were conducted on Monark 894E cycle ergometers. The HIIT protocol was based on a previous study that compared the time to exhaustion, safety, participant preference, and time spent near VO_{2peak} in older adults (58). For the first two-weeks, the HIIT protocol consisted of forty, 15 second intervals at 100% PPO interspersed with 15 seconds of passive recovery for a total exercise time of 20 minutes. Following a 5-minute passive recovery period, a second set of forty high-intensity intervals was completed (i.e., 40 minutes total exercise time). To adjust for anticipated aerobic fitness improvements, the duration of the HIIT protocol increased to 45 minutes (2 × 22.5 minutes; 2 × 45 intervals) for the remaining four weeks. A conservative tapering protocol was adapted from Berryman and colleagues (12) and incorporated to ensure appropriate recovery prior to the post-training assessment of MAP and VO_{2peak}. Specifically, the cycling intensity

was increased by 15W and training volume was decreased by 10 minutes (2 × 35 intervals) during the final two-weeks in preparation for the post-training testing.

The MICT protocol was based on the American College of Sports Medicine physical activity guidelines that recommend at least 30 minutes of daily moderate (40-60% VO_2max) aerobic physical activity (49). Continuous cycling at 60% PPO for ~34 minutes was initially prescribed. As previously employed (59), this duration was adjusted to ensure that the MICT protocol was isoenergetic to the HIIT protocol based on the assumption that mechanical efficiency, aerobic fitness and PPO were similar between groups; in that 20 total minutes at 100% PPO expends the same energy as 34 minutes at 60% PPO. To support this assumption, the HIIT and MICT groups demonstrated a similar VO_{2peak} and PPO (see Table 1 below). To accommodate the matched increase in energy expenditure, total exercise time was prolonged to 39 minutes for the remaining four weeks- and power output decreased by 15W during the last two weeks of MICT. The participants tapered in the last two training sessions of MICT by cycling at the same intensity (initial PPO + 15 Watts) for 30 minutes.

The RT protocol started with a 3-minute warm-up on a cycle ergometer at 25% PPO. Thereafter, participants completed a total of 8 strength exercises, alternating between muscle groups. The exercises were primarily isotonic machine-based and included leg press, bench press, hamstrings curl, shoulder press and leg extensions. Isotonic cable-exercises included seated row and latissimus pull-down, and bird-dogs (i.e., a core exercise that involves kneeling on the floor and simultaneously extending the hip while flexing the contralateral shoulder). Each participant performed 2 sets of 10 repetitions at 70% of estimated one repetition maximum (1-RM), based on perceived 1-

RM, for the first 2 weeks. Each exercise was performed with a duty cycle of an ~2 second concentric contraction followed by an ~2 second eccentric contraction. Both sets of each exercise were performed before starting the next exercise with 30-60 seconds of rest between sets. Upper- and lower-body exercises were alternated. Participants were instructed to increase the number of repetitions to 12 *ad libitum*. Once participants were able to perform 2 sets of 12 repetitions, the resistance was proportionally increased to a weight that equated to 10 repetitions of their new estimated 70% of 1-RM. Following each RT session, participants performed a 3-minute cool-down on a cycle ergometer at 25% PPO.

3.3.3 – Hemodynamics.

Heart rate (HR) was determined via cardiac intervals obtained from lead II of a bipolar electrocardiography configuration. Beat-by-beat systolic (SBP) and diastolic (DBP) blood pressures were measured using finger photoplethysmography (Portapres®; Finapres Medical Systems, Amsterdam, Netherlands). Brachial measurements of SBP and DBP were also recorded by an automated patient vital signs monitor (Carescape v100®, General Electric Healthcare) and used to calibrate the Portapres® waveform. All data were sampled continuously at 400 Hz using a PowerLab (PL3508 PowerLab 8/53, ADInstruments, Sydney, Australia) data acquisition system with the exception of the ECG waveform, which was sampled at 1000 Hz. Recordings were displayed in real-time and analyzed offline using LabChart software (ADInstruments, Sydney, Australia).

3.3.4 – Cardiovagal Baroreflex

Spontaneous BRS was assessed using the sequence method (14). Ten minutes of resting beat-by-beat SBP (via the Portapres®) and cardiac intervals were analyzed using

the open source Hemolab software (http://haraldstauss.com/HemoLab/HemoLab.php). This software detects sequences of 4 or more consecutive beats in which SBP and cardiac interval progressively increase (up sequence) or decrease (down sequence). The minimum beat-by-beat change required was both a 1 mmHg for SBP and 1 ms for R-R interval (76, 80). Linear regression related SBP to R-R interval for each sequence and only those with $r > 0.8$ were used (76, 80). For each participant, the average slope of the linear systolic blood pressure – R-R interval relationships for the pooled baroreflex sequences provided an index of cardiovagal BRS (ms/mmHg).

3.3.5 – Vascular Measures

Brachial and popliteal artery FMD assessments were used as indices of upper- and lower-limb vascular endothelial function (107, 129). The right BA and left POPA were imaged with participants in the supine and prone positions, respectively. The BA was imaged 3-5 cm proximal to the antecubital fossa and the POPA was imaged proximal to the bifurcation, at or slightly above the popliteal fossa. A pressure cuff attached to a rapid cuff inflation system (E20 and AG101, Hokanson®, Bellevue, WA) was positioned around the largest circumference of the forearm (BA; ~3 cm distal to the antecubital fossa) or calf (POPA; ~10 cm distal to the popliteal fossa POPA). All images were obtained using a 12-MHz multi-frequency linear array probe attached to a high-resolution ultrasound system (Vivid i, General Electric Healthcare). Simultaneous red blood cell velocity signals were recorded in duplex mode at a pulsed frequency of ~5 MHz and corrected with an insonation angle of 60° that remained constant throughout the study. The sample volume was adjusted for each participant such that the anterior to the posterior intima were included, as recommended in published guidelines (145).

Resting artery lumen diameter and red blood cell velocity were measured for a minimum of two minutes before inflation of the pneumatic cuff. The pressure cuff was then rapidly inflated to 250 mmHg for five minutes. Continuous arterial lumen diameter and red blood cell velocity recordings were collected throughout the cuff inflation period. Upon release of cuff pressure, lumen diameter and red blood cell velocity recordings continued for an additional five minutes. A minimum of 10 minutes separated the BA and POPA-FMD assessments to allow resting blood flow and shear rates to return to baseline levels.

In addition to FMD testing, the popliteal artery was imaged for 1-minute before and 10-minutes following a sublingual administration of nitroglycerin (0.4 mg), as an index of endothelial-independent vasodilation (24). A minimum 10 minutes of rest was provided between completion of the POPA-FMD assessments and the start of nitroglycerin-mediated dilation (POPA-NMD) testing.

3.3.6 – Data Analysis

Relative VO_2 data were averaged over 15-second intervals for the duration of the graded exercise protocol and divided by 3.5 ml/kg/min to calculate peak metabolic equivalents (Peak MET). SBP and DBP were determined from the Portapres® waveform as the maximum and minimum waveform values per heartbeat, respectively. These pressures were then used to calculate MAP using the equation ⅓ SBP + ⅔ DBP. In addition, Stroke volume (SV) was derived from the raw finger blood pressure waveforms using the validated ModelFlow® method (60, 79) incorporated into the proprietary Beatscope® software (version 1.1; TNO BMI, Amsterdam, the Netherlands). The finger used for recording blood pressure was maintained at heart level throughout the protocol

with participants in the supine position. Any minor deviations in height between heart level and the finger were corrected using the Portapres® height correction unit. Cardiac output (Q) was calculated as the product of HR and SV and total vascular conductance (TVC) as Q÷MAP. Portapres® data (SV, Q and TVC) were not recorded from two participants in the MICT group (1♂, 1♀) due to equipment malfunctions. A minimum of 10 minutes of resting supine data were used for BRS analysis and averaged for the hemodynamic measurements.

Video signals from the ultrasound were exported to a laptop via a video graphics array converter (Epiphan Systems Inc., VGA 2 USB, Ottawa) for offline analysis. Analysis of artery diameter, blood flow velocity and shear rate (i.e., frictional forces of blood flow on the endothelium) were performed using automated commercial edge-detection and wall-tracking software (FMD Studio, Cardiovascular Suite, Quipu, Pisa, Italy). Vascular measurements were completed by two different sonographers who demonstrated inter-tester coefficients of variation (CV) of 1.1%, 4.3% and 3.9% for baseline diameter, FMD% and NMD%, respectively. These CV values are consistent with previous research using automated edge-detection software (117).

Relative FMD was calculated using the equation: FMD (%) = (post-cuff deflation peak diameter – baseline diameter)/baseline diameter × 100%). Blood flow was calculated as mean blood flow velocity (cm/s) × 60 (s/min) × π × lumen radius^2 (cm^2). Leg (LVC) and forearm vascular conductance (FVC) were calculated by dividing POPA and BA blood flow by MAP, respectively. All blood flow and MAP data from the corresponding FMD-baseline periods were used for these calculations. Shear rate (SR, s^{-1}) was defined as [4 × Mean red blood cell velocity (cm/s)] / diameter (cm).

Subsequently, the SR area under the curve (SR_{AUC}) was calculated between the start of cuff deflation to the time that peak dilation occurred, which provides an indication of microvascular function. To minimize the individual vasodilatory response to reactive hyperemia, SR-normalized FMD has been recommended (103). However, neither BA-FMD or POPA-FMD were correlated to their respective SR_{AUC} response (BA-FMD: $r = 0.17$, $p = 0.46$; POPA-FMD: $r = 0.13$, $p = 0.55$), indicating the FMD-SR_{AUC} to be discouraged (5). As described by Atkinson and Batterham (6), allometric scaling of FMD is recommended to account for changes in arterial diameter. However, the relationship between the natural log of peak FMD diameter and resting diameter across time points and training groups yielded an unstandardized β-coefficient that did not deviate from 1 and had an upper 95% confidence interval that was >1, suggesting allometric scaling to be unnecessary in this present study (7). POPA-NMD was calculated as a percentage change from baseline to the peak lumen diameter obtained during the ten-minute period following sublingual administration of nitroglycerin.

3.3.7 – Statistical Analysis

Descriptive variables are presented as means ± standard deviations. Participant baseline and descriptive characteristics were compared using one-way analysis of variance (ANOVA). Baseline and within-training groups pre-post hemodynamic and vascular measurements were compared using a between-subjects (Group × Time) mixed ANOVA. A one-way ANOVA compared pre-post differences between the training groups. The variance of differences was assessed using Mauchly's test of sphericity. Bonferroni post-hoc testing was conducted on statistically significant ANOVAs. All data were assessed for normality using a Shapiro-Wilk test. All data were normally

distributed, and assumptions of sphericity were not violated. All statistics were completed in SPSS Version 23.0 (IBM, NY) statistical program. An estimated sample size of 14 participants was determined *a priori* based on previously reported changes in brachial artery FMD following 6-weeks of aerobic exercise training in young adults (129). Sample size calculations were also computed for training-induced changes that approached statistical significance (i.e., $0.05<p\leq0.10$) to determine the number of participants required to observe a statistically significant effect. Specifically, an effect size was calculated based on the means and standard deviations at baseline and following training using the power calculator program (G Power v3.1.3). This value was inputted into the power calculator and sample size was calculated using a dependent t-test design with an alpha error probability of 0.05 (i.e., Power = 0.95). Statistical significance was accepted as $p < 0.05$. All data are presented as means ± standard deviations (SD).

Chapter 4 – Results

4.1 – Participants

There were no baseline differences (all $p > 0.05$) in age, waist circumference, body mass index, VO_2peak or PPO between the training groups (Table 1). Following exercise training, participants in the HIIT and MICT groups had higher VO_2peak (both $p < 0.05$) and PPO (both $p < 0.001$), which were not observed following RT ($p > 0.08$). The estimated sample size needed for RT to result in a statistically significant improvement in PPO and VO_2peak was n=19 and n=21, respectively. Compared to RT, the increases in PPO were greater following HIIT ($p = 0.02$) and MICT ($p = 0.03$), as shown in Table 1.

Table 1. Participant demographic and descriptive characteristics.

	HIIT		MICT		RT	
	Pre-Training	Post-Training	Pre-Training	Post-Training	Pre-Training	Post-Training
Age (years)	66.2 ± 5.6		68.6 ± 7.4		66.3 ± 8.0	
Sex (Male, Female)	2♂, 4♀		3♂, 6♀		2♂, 6♀	
Body Mass Index (kg/m^2)	25.9 ± 3.7	25.8 ± 3.1	25.6 ± 4.0	25.5 ± 4.2	26.3 ± 3.6	25.9 ± 3.3
Waist Circumference (cm)	89.0 ± 11.4	88.8 ± 10.4	88.8 ± 10.8	90.1 ± 10.3	85.5 ± 11.0	84.5 ± 10.0
Heart Rate (beats/min)	71 ± 12	69 ± 10	69 ± 13	67 ± 11	67 ± 10	63 ± 9*
Stroke Volume (ml/beat)[a]	85 ± 20	88 ± 15	81 ± 23	83 ± 21	83 ± 25	89 ± 17
Cardiac Output (L/min)[a]	6.0 ± 1.3	6.0 ± 1.0	5.8 ± 1.8	5.8 ± 1.7	5.5 ± 1.9	5.5 ± 1.4
Systolic Blood Pressure (mmHg)	123 ± 14	120 ± 13	122 ± 12	120 ± 12	129 ± 9	125 ± 10
Diastolic Blood Pressure (mmHg)	71 ± 9	71 ± 11	72 ± 10	68 ± 8	70 ± 13	67 ± 11*
Mean Arterial Pressure (mmHg)	87 ± 9	86 ± 10	88 ± 10	85 ± 9	89 ± 11	85 ± 9
Total Vascular Conductance (ml/min/mmHg)[a]	69 ± 15	70 ± 13	69 ± 28	72 ± 29	64 ± 26	66 ± 19
Aerobic Fitness (mlO2/kg/min)	23.2 ± 4.1	28.5 ± 6.8*	22.0 ± 7.1	28.4 ± 7.1†	25.6 ± 11.1	27.6 ± 10.6
Peak METs	6.6 ± 1.2	8.1 ± 2.0*	6.3 ± 2.0	8.1 ± 2.0†	7.3 ± 3.2	7.9 ± 3.0
Peak Power Output (W)	157 ± 42	185 ± 49†	140 ± 37	167 ± 45†	143 ± 66	148 ± 67

Data are presented as means ± standard deviations. HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; RT, resistance training. *, $p < 0.05$ versus pre-training within same training group; †, $p < 0.001$ versus pre-training within same training group. [a]n = 7 for MICT group. A (training group × time) mixed ANOVA with Bonferroni post-hoc testing compared pre- versus post-training data within and between each group.

4.2 – Hemodynamics

All hemodynamics variables (HR, SV, SBP, DBP, MAP and TVC) were similar between the training groups at baseline ($p > 0.05$). SV, Q, SBP and MAP did not improve in any training group (all $p > 0.12$), as shown in Table 1. Resting HR was lower following RT ($p = 0.02$) and the decrease following MICT approached statistical significance ($p = 0.07$). An estimated sample size of $n = 90$ (effect size: 0.34) would be needed for the decrease in HR following MICT to be statistically significant. Additionally, DBP was lower following RT ($p = 0.03$) but was unchanged after HIIT and MICT (both, $p > 0.09$).

4.3 – Cardiovagal Baroreflex Sensitivity

There were no differences ($p > 0.05$) in the number of total sequences ('up' and 'down' combined) detected between the training groups at baseline (HIIT: 16.5 ± 8.0; MICT: 18.6 ± 10.2; RT: 12.1 ± 5.7). Furthermore, a similar number of sequences were used during both the baseline and post-training time for each group (all $p > 0.05$). A representative participants' baroreflex sequences is presented in Figure 4.3.1. Cardiovagal BRS was similar between all training groups at baseline ($p > 0.05$). A greater cardiovagal BRS was observed following HIIT ($p = 0.01$) and MICT ($p = 0.04$) but not RT ($p > 0.05$) (Figure 4.3.2).

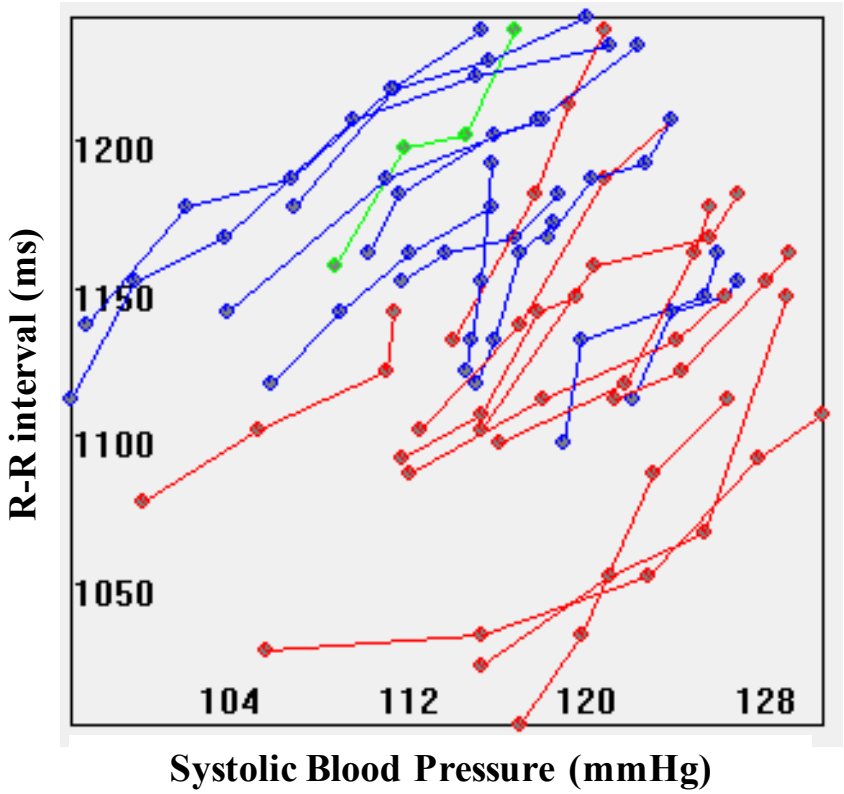

Figure 4.3.1: Representative participants' raw cardiovagal baroreflex data in which R-R interval and systolic blood pressure both progressively increase (up-sequence; red) or decrease (down-sequence; blue). Baroreflex sensitivity (ms/mmHg) was calculated as an average regression from all up and down sequences.

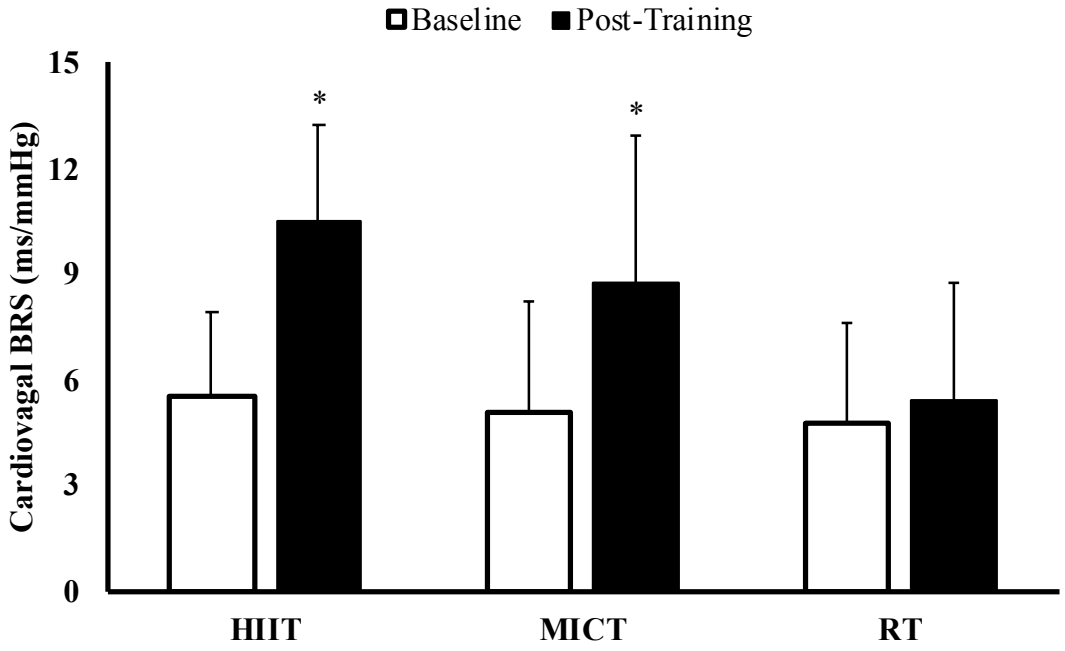

Figure 4.3.2: Cardiovagal baroreflex sensitivity (ms/mmHg) was similar at baseline for all training groups and increased following 6 weeks of HIIT and MICT only. Data are presented as means ± standard deviations. HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; RT, resistance training; *, $p < 0.05$ to baseline within same training group.

4.4 – Brachial Artery Hemodynamics and Function

Pre-training resting BA hemodynamics were similar between the training groups (all $p > 0.05$; see Table 2). Neither HIIT, MICT nor RT altered baseline diameter ($p > 0.11$). However, resting BA red blood cell velocity, blood flow and shear rate increased (all $p < 0.05$) following HIIT only. The pre-post differences in BA red blood cell velocity ($p = 0.04$) and shear rate ($p = 0.04$), but not blood flow ($p = 0.065$) were greater for HIIT in comparison to RT. An estimated sample size of $n = 16$ would be needed for the HIIT-induced improvements in BA blood flow to be statistically significant. HIIT was the only group in which FVC increased after training ($p = 0.04$).

HIIT and MICT augmented the BA-FMD response (both $p < 0.001$) with no change observed following RT (Figure 4.4). HIIT was the only training group to increase SR_{AUC} ($p = 0.04$; Table 2). Time to peak dilation did not change within or between the training groups (Table 2).

Table 2. Comparison of brachial artery parameters across the HIIT, MICT and RT protocols

	HIIT		MICT		RT	
	Pre	Post	Pre	Post	Pre	Post
Resting						
Diameter (mm)	4.47 ± 0.96	4.46 ± 0.94	3.84 ± 0.53	3.85 ± 0.56	3.72 ± 0.70	3.77 ± 0.72
RBC Velocity (cm/s)	10.8 ± 3.0	13.1 ± 3.4†	12.9 ± 5.3	12.9 ± 4.5	13.4 ± 5.7	12.1 ± 5.0
Blood Flow (ml/min)	100 ± 34	116 ± 24*	90 ± 40	93 ± 45	84 ± 39	78 ± 33
Shear Rate (s^{-1})	102 ± 39	126 ± 50†	137 ± 66	135 ± 53	150 ± 67	136 ± 63
FVC (ml/min/mmHg)[a]	1.17 ± 0.41	1.37 ± 0.32*	1.05 ± 0.62	1.11 ± 0.72	0.97 ± 0.47	0.91 ± 0.37
Flow-Mediated Dilation						
Absolute FMD (mm)	0.20 ± 0.10	0.33 ± 0.12†	0.18 ± 0.09	0.29 ± 0.10†	0.18 ± 0.08	0.21 ± 0.07
SR_{AUC}	11791 ± 4028	14534 ± 5524*	12700 ± 5647	14094 ± 3900	13066 ± 2656	15305 ± 3965
Time to Peak Dilation (s)	54 ± 16	56 ± 16	69 ± 23	70 ± 19	62 ± 17	65 ± 14

Data are presented as means ± standard deviations. HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; RT, resistance training; RBC, red blood cell; FVC, forearm vascular conductance; FMD, flow-mediated dilation; SR_{AUC}, shear rate area under the curve to peak dilation. *, $p < 0.05$ to pre-training within training group; †, $p < 0.001$ to pre-training within exercise modality. [a]n = 7 for MICT group. A (training group × time) mixed ANOVA with Bonferroni post-hoc testing compared pre- versus post-training data within and between each group.

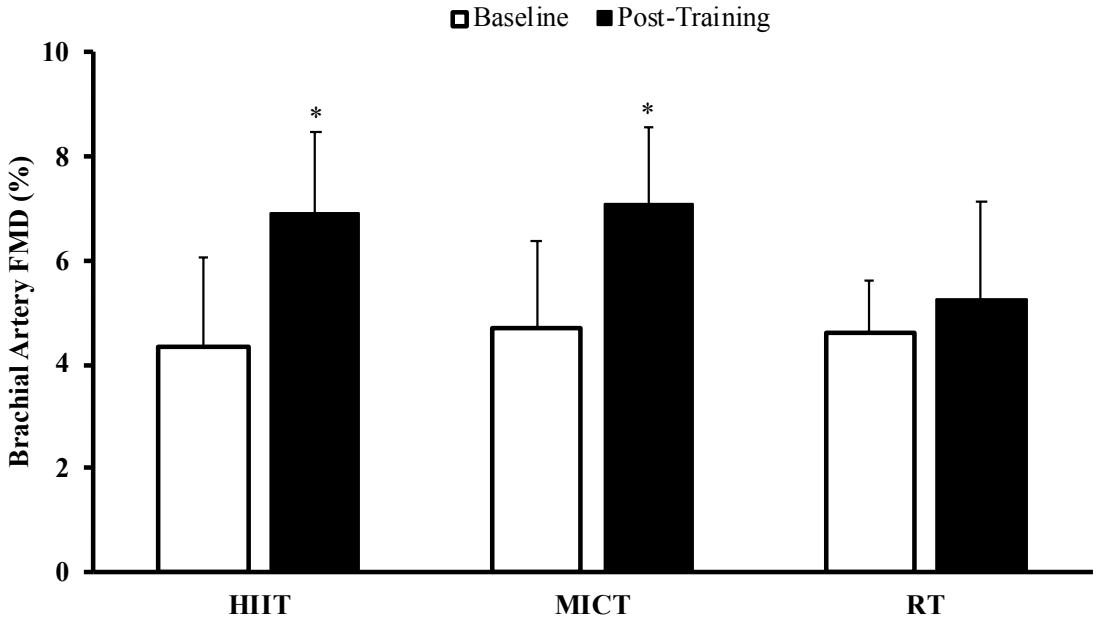

Figure 4.4: Brachial artery relative flow-mediated dilation (FMD) was similar between training groups at the baseline time point and increased following 6-weeks of HIIT and MICT only. Data are presented as means ± standard deviations. HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; RT, resistance training; *, $p < 0.05$ to baseline within same training group.

4.5 – Popliteal Artery Hemodynamics and Function

Pre-training resting POPA measurements were similar between HIIT, MICT and RT groups (all $p > 0.05$; Table 3). Resting POPA diameter was larger following RT ($p = 0.007$) but remained unchanged after HIIT or MICT ($p > 0.05$; Table 3). Resting POPA red blood cell velocity, blood flow, shear rate and LVC did not increase following any of the training programs (all $p > 0.05$; Table 3).

Both relative- and absolute POPA-FMD improved following HIIT and MICT (all $p < 0.001$; Figure 4.5). The training-induced changes in POPA-FMD were similar between HIIT and MICT ($p > 0.05$), which were both higher than RT (both $p < 0.001$; Figure 4.5). POPA SR_{AUC} responses increased in all three groups (HIIT: $p = 0.001$; MICT: $p = 0.001$; RT: $p = 0.002$; Table 3). Baseline relative- and absolute POPA-NMD

were similar between all groups and remained unchanged following all short-term training programs ($p > 0.22$; Table 3).

Table 3. Comparison of popliteal artery parameters across the HIIT, MICT and RT protocols

	HIIT		MICT		RT	
	Pre-Training	Post-Training	Pre-Training	Post-Training	Pre-Training	Post-Training
Resting						
Diameter (mm)	6.20 ± 1.48	6.20 ± 1.50	6.35 ± 1.92	6.33 ± 1.91	6.76 ± 0.79	6.89 ± 1.91*
RBC Velocity (cm/s)	4.8 ± 1.7	4.9 ± 1.8	3.3 ± 1.7	4.0 ± 1.7	3.9 ± 2.6	4.0 ± 2.2
Blood Flow (ml/min)	92 ± 47	90 ± 47	61 ± 30	73 ± 38	84 ± 45	87 ± 38
Shear Rate (s^{-1})	34 ± 20	34 ± 21	23 ± 16	28 ± 16	24 ± 17	24 ± 15
LVC (ml/min/mmHg)[a]	1.04 ± 0.50	1.02 ± 0.45	0.82 ± 0.26	1.04 ± 0.51	0.99 ± 0.63	1.05 ± 0.52
Flow-Mediated Dilation						
Absolute FMD (mm)	0.19 ± 0.22	0.27 ± 0.16*	0.12 ± 0.06	0.21 ± 0.09†	0.19 ± 0.17	0.20 ± 0.16
SR_{AUC}	6316 ± 2684	8560 ± 3784*	4751 ± 2490	6738 ± 3095*	4987 ± 2311	6874 ± 3169*
Time to Peak Dilation (s)	119 ± 23	119 ± 15	107 ± 17	103 ± 19	99 ± 29	96 ± 23
Nitroglycerin-Mediated Dilation						
Relative NMD (%)	4.92 ± 1.95	5.16 ± 1.49	5.13 ± 1.90	5.52 ± 1.77	4.35 ± 2.25	4.14 ± 1.62
Absolute NMD (mm)	0.32 ± 0.20	0.33 ± 0.16	0.32 ± 0.08	0.33 ± 0.07	0.31 ± 0.18	0.31 ± 0.14

Data are presented as means ± standard deviations. HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; RT, resistance training; RBC, red blood cell; LVC, leg vascular conductance; FMD, flow-mediated dilation; SR_{AUC}, shear rate area under the curve to peak dilation; NMD, nitroglycerin-mediated dilation. *, $p < 0.05$ to pre-training within training group; †, $p < 0.001$ to pre-training within training group. a, $n = 7$ for MICT group. A (training group × time) mixed ANOVA with Bonferroni post-hoc testing compared pre- versus post-training data within and between each group.

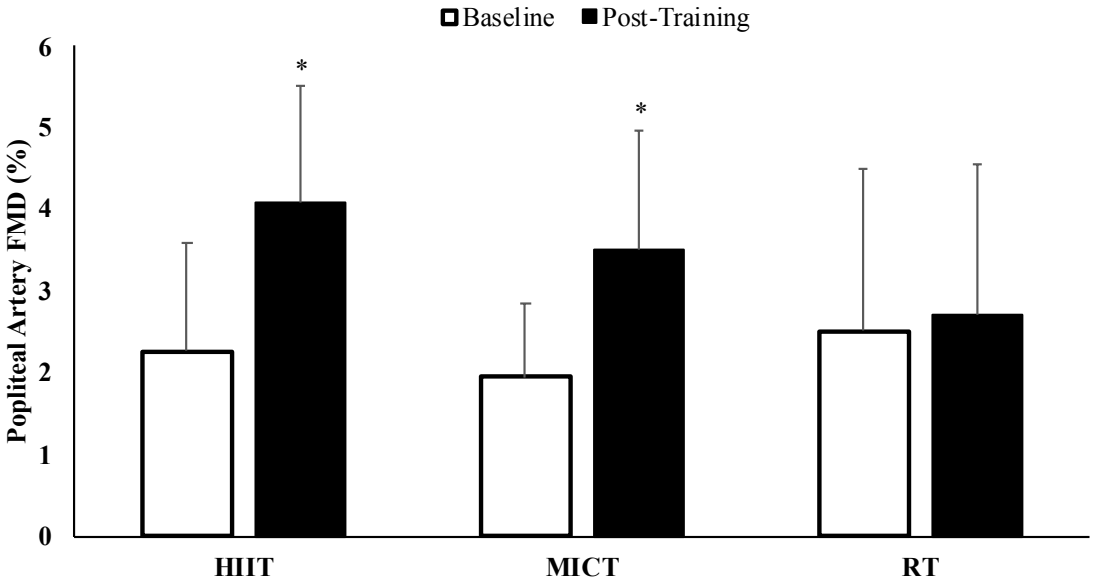

Figure 4.5: Popliteal artery relative flow-mediated dilation (FMD) was similar at baseline between the groups at the baseline time point and increased following 6-weeks of HIIT and MICT only. Data are presented as means ± standard deviations. HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; RT, resistance training; *, $p < 0.05$ to baseline within same training group.

Chapter 5 – Discussion

The purpose of this study was to compare changes in cardiovagal baroreflex sensitivity, as well as, vascular function in the brachial and popliteal arteries following short-term HIIT, MICT and RT in older adults. Contrasting with our hypothesis, six-weeks of HIIT and MICT similarly augmented cardiovagal BRS and endothelial-dependent dilation in the brachial and popliteal arteries. Furthermore, RT did not improve BRS nor vascular endothelial function in either artery. POPA SR_{AUC} (i.e., index of microvascular function) was greater following exercise training in all three groups. However, BA microvascular function was only increased following HIIT. Favorable increases in resting blood flow and vascular conductance were also observed in both the BA and POPA following HIIT, but not after MICT or RT. This is the first study to compare high-intensity interval versus moderate-intensity continuous aerobic exercise training, and to document resistance training–induced vascular adaptations in an older population.

The current findings demonstrated that six-weeks of HIIT and MICT elicited similar, favorable changes in spontaneous cardiovagal BRS in older adults that were not observed in the RT group. While 12-weeks of MICT (86) and 14-weeks of HIIT (110) have separately been shown to increase cardiovagal BRS in elderly persons, the present study is the first to concurrently assess both HIIT and isocaloric MICT in this population and highlights that spontaneous BRS may be improved in as little as 6-weeks of training. The findings of Collier et al. (28) in pre-hypertensive middle-aged adults support this finding. Specifically, they observed improved cardiovagal BRS (from 6.7 to 7.9 ms/mmHg) following 4-weeks of training (3 days/week) that involved 30 minutes of

treadmill exercise at 65% of VO_2peak. Additionally, Collier et al. (27) did not observe BRS changes following their whole-body RT protocol (9 exercises for 3 sets of 10 repetitions, 3 days/week), which is consistent with our results (Figure 4.3.2). In summary, it appears that aerobic exercise is more effective than RT in modulating cardiovagal BRS in this population, which is indicative of improved beat-by-beat blood pressure control and has been linked to an associated reduced risk of total cardiac mortality (119).

This study was not designed to investigate the mechanisms associated with exercise-induced changes in cardiovagal BRS. However, they may have been attributed to an aerobic exercise-induced increase in the compliance of large cardiothoracic arteries (i.e., ascending aorta and carotid sinus) where the baroreceptors are located (89, 90). Additionally, intravenous infusion of antioxidants (i.e., ~4 grams of ascorbic acid) has been shown to increase cardiovagal BRS in older, but not younger persons (92). Further, antioxidants have been shown to influence baroreflex function at multiple sites in the baroreflex arc. Specifically, antioxidants have been shown to increase barosensory arterial wall distensibility (94) and prevent the inhibition of baroreceptor firing caused by free radicals (78). It is possible that HIIT and MICT, but not RT, decreased the levels of oxidative stress in our sample of older adults which may be responsible for the enhanced BRS. Certainly, future mechanistic research is warranted to confirm or refute this hypothesis.

Our results support the notion that beneficial vascular adaptations occur following short-term aerobic exercise training in older adults, which may help attenuate the known deteriorating effects of advanced aging (41) including chronic low grade inflammation and increased oxidative stress (153). Adding to the current body of literature, our short-

term (i.e., 6-weeks) HIIT and MICT models (but not RT) elicited a sufficient stimulus for modifying BA-FMD. As identified in a recent meta-analysis (4), RT and aerobic training ≥4 weeks typically increase the relative BA-FMD (%) of older adults by 1.8% and 2.9%, respectively. Such improvements are similar to those observed in the present study for aerobic training (HIIT: 2.6%; MICT: 2.4%) but not for our RT program (~0.7%) (see Figure 4.4). Of particular relevance, a 1% increase in relative BA-FMD confers a 13% reduction in the risk of experiencing negative cardiovascular events (65). Furthermore, Ashor and colleagues demonstrated that a 2 MET (7.0 ml/kg/min) increase in VO_2peak corresponds to a 1% increase in BA-FMD (4), whereas we observed a ~2.5% greater relative BA-FMD with only a ~1.5 MET improvement following HIIT and MICT (Table 1 & Figure 4.4). Herein, both HIIT and MICT resulted in a clinically significant reduction in the risk of having a future cardiovascular event in a relatively short period of training.

Of relevance, we did not observe any changes in POPA-NMD following HIIT, MICT or RT. Overall, this suggests that longer training periods may be needed to combat the diminished POPA vascular smooth muscle sensitivity associated with advancing age (107). This finding is consistent with other studies conducted in older adults that investigated exercise training-induced changes in BA-NMD modalities using shorter [e.g., 2 weeks; (70)] or longer [e.g., 12-weeks (32, 122, 152)] training durations.

One proposed mechanism behind the improved relative BA-FMD and POPA-FMD responses is the augmented SR_{AUC} responses following exercise training; shear rate being the stimulus responsible for the production of NO. However, the relationship between SR_{AUC} and BA-FMD is weak, if present at all, in older adults (148).

Additionally, a paucity of research has examined the SR-FMD relationship in the popliteal artery. We observed an increased BA-FMD without an associated increase in BA-SR_{AUC} following MICT (Fig 4.4, Table 2). Similarly, there was no increase in relative POPA-FMD following RT despite a greater POPA-SR_{AUC} (Fig. 4.5, Table 3). A more likely mechanism for the higher FMD in the upper- and lower-limb arteries following HIIT and MICT is a reduction in oxidative stress (i.e., ROS). Aging is associated with exacerbated oxidative stress that promotes the uncoupling of endothelial nitric oxide synthase (37), which may be attenuated following exercise training (120). Reductions in ROS levels have also been linked to more favorable microvascular responses (125), further supporting this proposed mechanism. Future studies are needed to confirm or refute this hypothesis. Additionally, Rossman et al. (118) recently demonstrated cellular senescence (i.e., irreversible growth arrest of a cell) to be a key mechanism in age-related vascular dysfunction using a cross-sectional comparison of active and sedentary older adults. As such, interventional studies should investigate the role of different exercise modes and intensities on these cellular stressors such as oxidative stress, DNA damage, dysfunctional telomeres or metabolic stimuli that induce cell arrest in combatting the age-associated effects on macrovascular and microvascular function.

With advancing age there is a reduction in peripheral blood flow (126). Interestingly, HIIT, but not MICT or RT, resulted in a greater resting BA blood flow and shear stress through an increase in red blood cell velocity with no corresponding change in BA diameter. Anterograde BA red blood cell velocity is positively associated with physical function in older persons (31) and a higher resting shear stress may promote

anti-atherogenic gene expression (77). This suggests our HIIT protocol may be a more effective training program than MICT in combatting the decline in physical function and progression of atherosclerosis in aged populations.

POPA diameter was greater following RT but not following either of the aerobic training protocols. Perhaps the time-course for structural adaptations to RT occurs at a faster rate than aerobic training, which may explain why we observed an increase in POPA diameter without a corresponding change in POPA-FMD. With that, the criteria for allometric scaling was not met following RT with the regression slope between the logarithmically transformed baseline and peak POPA diameters not deviating from 1 and the upper 95% CI being > 1 [unstandardized β-coefficient = 1.13 (95% CI: 1.01-1.25)], indicating that peak diameter increased as a constant proportion of resting diameter. Additionally, vascular tone is regulated by many factors, limiting vessel diameter as a comprehensive measure of vascular structure (149). Future studies investigating such changes should incorporate a combination of nitroglycerin administration, forearm or calf ischemia, and ischemic exercise as this may be more accurate representation of maximal dilatory capacity (96). Making these additional measurements would permit the determination of an artery's true peak dilatory capacity and would provide further insight into the effects of short-term exercise-induced structural adaptations.

It is possible that RT reduced sympathetic nervous system activity given the corresponding decrease in HR. If so, this would have removed a potent vasoconstrictor signal resulting in vasodilation. However, only one longitudinal RT study to date has measured muscle sympathetic nerve activity (MSNA) in which 8 weeks of whole-body RT lowered SBP and DBP but did not alter MSNA in young adults (age 21±1 years) (19).

Currently, the effects of short-term (e.g., 6-weeks) RT on MSNA in older populations is unknown. The decrease in HR following RT may also be related to greater vagal modulation on the sinoatrial node, which has been shown following 10-weeks of progressive strength training in young to middle-aged adults (63). Other studies demonstrated no change in parasympathetic activity following 10 or 21 weeks (67) or six-months (85) of RT in older adults. Our study did not observe an increase in cardiovagal BRS, despite a decrease in resting HR following RT. Previous studies have demonstrated an improvement in cardiovagal BRS without associated changes in SBP or HR following 12-weeks of aerobic training in an older populations (86, 91), which is consistent with our HIIT and MICT groups. Conversely, other exercise training studies in this population have observed concurrent decreases in resting HR and increases in BRS in older populations (28, 110). Given our measure of cardiovagal BRS assessed the relationship between spontaneous fluctuations in resting HR and SBP (ms/mmHg), it is possible that there was an increase in blood pressure variability following RT that would offset the decrease in HR which warrants further inquiry.

As previously mentioned, a 1% improvement in BA-FMD confers a 13% reduced risk of having a future cardiovascular event (65). Using this relationship, the aerobic training groups reduced the risk of a cardiovascular event by ~33% (BA-FMD increased by ~2.5% following MICT and HIIT). While such a relationship does not exist for the POPA, vascular function largely improved (~1.7%) following aerobic training in the vascular bed that is responsible for supplying the active muscle and is the site of atherosclerotic development (35). MICT and HIIT, but not RT resulted in an increased cardiovagal BRS suggesting an enhanced ability to regulate blood pressure. This may

translate to a reduced risk of arterial hypertension, which is a key characteristic of cardiovascular disease development (157). Future studies should include patients with cardiovascular disease who have impaired vascular function and blood pressure control to investigate the potential prognostic value of training-induced increases in POPA-FMD.

5.1 – Limitations

Although improvements in BA-FMD were observed, endothelial-independent dilation was not assessed in the BA. However, it is unlikely that six-weeks of training was long enough to enhance vascular smooth muscle function in the BA (4). The results of this study may be limited by sample size (HIIT: n=6; MICT: n=9; RT: n=8) but our numbers are reflective of previous studies that compared vascular response to different forms of aerobic exercise training in younger adults (129, 159). Additionally, statistical significance was achieved in our measures of BRS and vascular reactivity that would likely be unchanged with the addition of more participants. However, there were a number of measures that approached statistical significance that, with a greater sample size (~20 per group), may further corroborate our main findings. Furthermore, sex-differences in the vascular responses to exercise training may exist (111). However, the number of men and women in the three exercise groups were similar. Future studies should examine the role that sex has on exercise mode- and aerobic exercise intensity-induced vascular responses in both younger and older populations.

We acknowledge our study did not include a control group, but our repeated measures design allowed participants to serve as their own controls. As well, randomized controlled studies investigating exercise modalities and endothelial function consistently demonstrated no improvement in the control group (4), which, in conjunction with the

high-reproducibility of our ultrasound measures suggest the lack of a control group to be a minor limitation that would not alter the main findings of this study. Lastly, future research should investigate the role that exercise mode and aerobic exercise intensity have on other factors known to influence vascular health in aged individuals such as oxidative stress (37) and potent vasoconstrictors [e.g., endothelin-1; (38)].

5.2 – Conclusion

The findings of this study demonstrated that 6-weeks of HIIT and MICT are superior to RT at eliciting changes in cardiovagal BRS and endothelial-dependent dilation in the brachial and popliteal arteries of older adults. Despite being the only training modality to not improve aerobic fitness, an increase in popliteal artery diameter was observed following RT that was not apparent in the HIIT or MICT groups. However, HIIT resulted in greater resting blood flow and shear rate in the BA. Future studies should incorporate more frequent measures to reveal the temporal trends of different training models and their respective shear stress profiles in determining the time-course of functional and subsequently structural arterial responses in aged populations.

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Appendix A – REB Approval

DALHOUSIE UNIVERSITY
Research Services

Health Sciences Research Ethics Board
Letter of Approval

July 26, 2017

Myles O'Brien
Health\Health & Human Performance

Dear Myles,

REB #: 2017-4196
Project Title: Vascular Health: The Impact of Different Exercise Modalities in Older Adults

Effective Date: July 26, 2017
Expiry Date: July 26, 2018

The Health Sciences Research Ethics Board has reviewed your application for research involving humans and found the proposed research to be in accordance with the Tri-Council Policy Statement on *Ethical Conduct for Research Involving Humans*. This approval will be in effect for 12 months as indicated above. This approval is subject to the conditions listed below which constitute your on-going responsibilities with respect to the ethical conduct of this research.

Sincerely,

[redacted]

Dr. Tannis Jurgens, Chair