PHYSICAL ACTIVITY AND VASCULAR HEALTH IN ADULTS WITH CP

RELATIONSHIPS BETWEEN MOTOR CLASSIFICATION, PHYSICAL ACTIVITY AND CARDIOVASCULAR HEALTH IN ADULTS WITH CEREBRAL PALSY

By

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A Thesis Submitted to the School of Graduate Studies

in Partial Fulfillment of the Requirements for

the Degree Masters of Science in Kinesiology

McMaster University MASTER OF SCIENCE (2014)

Hamilton, Ontario (Kinesiology)

TITLE: Relationships between motor classification, physical activity and cardiovascular health in adults with cerebral palsy

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NUMBER OF PAGES: xv, 110

**ABSTRACT**

Cerebral palsy (CP) is a disability that impacts a person throughout their lifespan and may place adults with the condition at an increased risk of physical inactivity and cardiovascular disease. Cardiovascular structure and function in adults with CP has not been comprehensively investigated previously. In the current cross-sectional, observational study, endothelial function, carotid distensibility, and arterial stiffness were assessed using flow-mediated dilation (FMD), B-mode ultrasound, and pulse wave velocity (PWV), respectively, in forty adults with CP (age 33.7 ± 12.7 years). The study sample was separated based on whether subjects were community ambulant or community non-ambulant using the Gross Motor Function Classification System (GMFCS). Those in GMFCS I-II were labeled community ambulant (age 31.7 ± 10.4 years) while those in GMFCS III-V were community non-ambulant (age 34.8 ± 13.6 years). Resting arterial stiffness was examined through assessment of central and upper and lower limb peripheral PWV (cPWV, uPWV, lPWV). Carotid intima-media thickness (IMT), a measure of vascular structure, was also quantified using B-mode ultrasound images and a semi-automated edge detection software program. cPWV was calculated using the distance (carotid to femoral using the subtraction method) and time delay between the foot of the carotid waveform and the foot of the femoral waveform. uPWV was calculated from the carotid to radial artery distance (subtracting the distance from the carotid to sternal notch from the carotid to radial distance) and the time delay between the arrival of the foot of each corresponding waveform. lPWV was calculated from the femoral to posterior tibialis artery using the distance between each site and time delay between the arrival of the foot of each corresponding waveform. Physical activity (PA) levels were assessed using Actigraph accelerometry with cut points that had been previously determined in normal adults. Cardiometabolic markers of fasting serum interleukin-6, insulin, glucose, and a lipid panel were analyzed. The non-ambulant group had an increased uPWV (10.2 m/s ± 1.9) compared to the ambulant group (8.28 m/s ± 1.6) (p<0.01) despite no differences in cPWV or lPWV. There were no group differences (p>0.05) in absolute, relative or normalized FMD responses. Both groups also had similar values of carotid IMT and carotid distensibility. No group differences were found in any of the cardiometabolic or inflammatory markers. Moderate-to-vigorous PA (MVPA) levels were greater in the ambulant group (2.4 mins ± 2.1 per hour) compared to the non-ambulant group (0.3 mins ± 0.6 per hour) (p<0.01). Furthermore, sedentary time was greater in the non-ambulant group (57.8 mins ± 1.9 per hour) compared to the ambulant group (51.6 mins ± 4.7 per hour) (p<0.01). Despite differences in PA levels, MVPA was not a significant independent predictor of vascular or metabolic health in this cohort of adults with CP. However, GMFCS level was predictive of both uPWV and resting heart rate. Future research should include adults with CP who are older in age to gain further insight into the potential consequences of an activity-limited lifestyle (specifically in the non-ambulant group) on cardiovascular and metabolic health in this clinical population.

**ACKNOWLEDGMENTS**

I would like to thank my supervisor, Dr. Maureen MacDonald for her guidance, knowledge and support over the past two years. Although you were “across the pond” last year, you were always quick to respond to emails and meet through Skype whenever needed. Your edits of manuscripts, abstracts, and thesis documents have allowed me to enhance my skills in research writing – something that I lacked confidence in when starting my masters degree. I would like to thank the members of my committee, Dr. Timmons and Dr. Gorter for their insight and research expertise with this project. I would also like to thank Dr. Bentley and the staff at the Comprehensive Spasticity Management Program for assisting with participant recruitment. All of you have made this research project a positive learning experience.

I would like to thank the members of the Vascular Dynamics Laboratory for their assistance with data collection and offering to go for much needed “coffee breaks” throughout long days of data analysis. I grew up playing competitive hockey and was excited when I was able to work in such a team oriented research setting. I would also like to acknowledge the adults with cerebral palsy who participated in this project. You truly made this research a rewarding experience. It was an honour to learn that you were so grateful that this research was being conducted in such an understudied clinical population.

Finally, I would like to thank my family, friends, and significant other, Vanessa. The continued support through my educational journey helps to remind me that there is a light at the end of the tunnel – and that all of this hard work is worth it.

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**LIST OF ALL ABBREVIATIONS AND SYMBOLS**

BMI Body mass index

cIMT Carotid intima-media thickness

CP Cerebral Palsy

CRP C-reactive protein

CVD Cardiovascular disease

DBP Diastolic blood pressure

FMD Flow-mediated vasodilation

GMFCS Gross motor function classification system

HDL High-density lipoprotein

LDL Low-density lipoprotein

LV Left ventricle

MI Myocardial infarction

MVPA Moderate-to-vigorous physical activity

NO Nitric Oxide

NOS Nitric oxide synthase

PA Physical activity

PP Pulse pressure

PTT Pulse transit time

PWV Pulse wave velocity

SBP Systolic blood pressure

TC/HDL-C Total cholesterol to HDL cholesterol ratio

WC Waist circumference

**CHAPTER 1**

**LITERATURE REVIEW**

***Introduction***

Cardiovascular disease (CVD) is a disorder of the heart and blood vessels and includes diseases such as coronary heart disease, cerebrovascular disease, and peripheral artery disease. CVD is the number one cause of death worldwide [[1](#_ENREF_1)]. It was estimated that 17.3 million people died from CVD in 2008, which was representative of 30% of all global deaths. This number is expected to increase to 23.3 million by 2030 [[2](#_ENREF_2)]. Many CVDs can be prevented by addressing behavioural risk factors such as smoking, poor diet, and physical inactivity [[3](#_ENREF_3)]. Lifestyle modifications such as moderate increases in physical activity (PA) have proven to have protective effects against the influence of traditional risk factors of CVD [[4](#_ENREF_4)].

Aerobic exercise can improve many of the classical risk factors that are associated with elevated CVD such as body fatness, insulin resistance, and blood pressure, however the dose response curve for the relationship between exercise and each risk factor varies [[5](#_ENREF_5)]. It is estimated that up to 30-40% of the CVD risk reduction associated with increased activity is not explained by traditional risk factors [[6](#_ENREF_6), [7](#_ENREF_7)]. Structural and functional adaptations to the vascular wall associated with exercise, such as decreased wall thickness, increased elastin content and the attenuation of collagen progression within the arterial wall and changes in endothelial function may also be involved in exercise related CVD risk reduction [[8](#_ENREF_8)].

Cerebral palsy (CP) is a cause of disability that impacts a person across their lifespan and may consequently limit the amount of PA that this population can endure [[9](#_ENREF_9)]. Particularly, adults with CP are likely not engaging in sufficient PA to produce improvements in fitness required to experience positive health benefits [[10](#_ENREF_10)]. Regarding causes of mortality, many more deaths have been attributed to diseases of the respiratory and circulatory system in adults with CP aged 20-50, compared to the general population, and these are typically more pronounced in the more severely affected [[11](#_ENREF_11)]. Perhaps the lack of PA in these individuals living with a disability may be compromising their cardiovascular health.

In addition to the potential predictive benefit of indices of vascular health, other emerging risk markers such as PA levels and biomarkers of inflammation and metabolism may provide useful information about CVD risk in special populations at elevated risk.

**1.1 VASCULAR MARKERS OF CVD RISK**

**1.1.1 *Arterial system***

The systemic arterial system serves to disperse blood at high pressures to peripheral vascular sites at rates required to meet tissue metabolic requirements [[12](#_ENREF_12)]. The arterial system can essentially be separated into 3 anatomical regions with each having a distinct and individual function: (1) The large elastic arteries (aorta, iliac, carotid) serve as a buffering reservoir to transform pulsatile blood flow into continuous flow in order to perfuse the smaller arteries, arterioles, and capillaries. To do this, these elastic arteries passively expand and thereby store the blood ejected from the left ventricle (LV) during systole, and recoil to propel the blood away from the heart during diastole; (2) The muscular peripheral arteries modify the speed of travel of pressure and flow waves along their length by altering their smooth muscle tone. These peripheral arteries also determine when reflected pressure waves arrive back at the heart based on both bifurcation sites and impedance; and (3) The arterioles, by modifying their diameter, alter peripheral resistance and aid in the maintenance of mean arterial blood pressure in the face of increased or decreased flow [[12](#_ENREF_12)].

**1.1.2 *Arterial anatomy***

An artery can be described as a viscoelastic tube in which the diameter fluctuates with a pulsating pressure that is created by the oscillating flow generated through the cardiac cycle [[13](#_ENREF_13)]. The predominant structural materials of the arterial wall are collagen and elastin. The arterial wall is divided into three distinct regions: the intima, media, and adventitia. The intima consists of the vascular endothelium and a thin layer of elastin and collagen that anchors the intima to the internal elastic lamina; which separates the intima from the media layer. The media is the determinant of the mechanical properties of a blood vessel and is comprised of smooth muscle cells that run parallel to elastin fibers. The outer layer of the vascular wall, the adventitia, is mainly formed from collagen and elastin and merges with the surrounding connective tissue. The distribution of elastin and collagen is significantly different between the central and peripheral arteries. In the proximal aorta, elastin dominates, whereas in the distal peripheral arteries collagen is more pronounced [[13](#_ENREF_13)].

**1.1.3 *Carotid intima-media thickness***

Carotid intima-media thickness (cIMT) is an index of arterial structure and represents a composite of intima and medial wall thickness [[14](#_ENREF_14)]. Increases in cIMT have been shown to correlate to atherosclerosis in the coronary arteries [[15-17](#_ENREF_15)] and peripheral arteries. The presence of a traditional CVD risk factor(s) is positively associated with an increased cIMT [[18](#_ENREF_18)]. A study conducted in middle-aged Finnish men reported that an increase of 0.1mm in far wall cIMT was associated with an 11% increased risk of myocardial infarction (MI) [[19](#_ENREF_19)]. Furthermore, a cIMT greater than 0.82mm increases the risk of MI, stroke, and peripheral arterial disease [[20](#_ENREF_20)]. With regards to traditional CVD risk factors, obesity was the strongest predictor of cIMT in healthy and non-healthy individuals (mean age 34 years) [[21](#_ENREF_21)]. However, in a more recent study, it was discovered that age was the strongest predictor of increased cIMT [[22](#_ENREF_22)]. As cIMT is an independent predictor of incidental stroke, the literature has shown that increases in PA can attenuate the progression of stroke. However, it is uncertain as to whether this is a direct effect of a reduction in cIMT. Tanaka and colleagues showed that there was no difference in cIMT between healthy sedentary and endurance trained individuals within the same age group. Furthermore, 3 months of an exercise intervention did not reduce cIMT in the sedentary group [[23](#_ENREF_23)]. Perhaps exercise mediates its prevention of stroke through other avenues apart from reductions in cIMT.

CIMT is measured from B-mode ultrasound images of the arterial far wall that include two detectable lines representing the boundaries of the lumen-intima interface and the media-adventitia interface [[24](#_ENREF_24)]. Reproducibility of cIMT measurements has improved over the years, with measurement error decreasing from 25-40% to a current level of 10-20% [[25](#_ENREF_25)].

**1.1.4*****Arterial stiffness***

Measures of arterial stiffness predict the inherent ability of an artery to expand and contract with cardiac contraction and relaxation [[26-28](#_ENREF_26)]. Arterial stiffness is determined by structural and functional components that relate to the intrinsic structural properties of the artery [[26](#_ENREF_26), [27](#_ENREF_27)]. The elastic properties of an artery are the qualities that enable the artery to be stretched while retaining its ability to return to the original form when the pressure (or stressor) is removed [[28](#_ENREF_28)]. The endothelium, elastin fibers, and smooth muscle are all contributors to arterial stiffness [[28](#_ENREF_28)]. At low and normal pressures, the elastin fibers in the arterial wall bear most of the stress whereas at increased pressure (> 200mmHg) collagen fibers are involved in the mediation of stiffness and protect against arterial rupture [[29](#_ENREF_29)]. Differences in the ratio of elastin to collagen in the arterial wall can affect stiffness as the lower the ratio, the stiffer the artery [[30](#_ENREF_30)]. Elevated smooth muscle tone increases arterial stiffness as a result of increased alpha-adrenergic receptors promoting smooth muscle contraction through increased sympathetic activation [[31](#_ENREF_31)].

It has been shown that arteries become stiffer with increasing age and cardiovascular related diseases such as hypertension, diabetes, and atherosclerosis [[32](#_ENREF_32)]. Structural changes that contribute to increased arterial stiffness include fragmentation of elastin, increased deposition of collagen, arterial calcification, inflammation, and cross-linking of collagen molecules [[33](#_ENREF_33), [34](#_ENREF_34)]. Arterial stiffness and resultant wave reflections are an important determinant of increasing systolic and pulse pressure (PP) in the aging community [[35](#_ENREF_35)]. These increases in pressure lead to the development of cardiovascular complications and events, including stroke and MI [[34](#_ENREF_34)].

Increases in arterial stiffness cause a premature return of the reflected wave in late systole, resulting in increases in PP and thus systolic blood pressure (SBP) [[13](#_ENREF_13)] which is also referred to as augmentation index. Elevations in SBP increase the afterload on the LV, as the LV must now contract harder to overcome the increased central PP. With the LV subsequently working harder, arterial stiffness is thus associated with LV hypertrophy, a known risk factor for coronary events in normotensive and hypertensive patients [[36](#_ENREF_36)].

**1.1.5*****Further causes of increasing arterial stiffness***

The literature has documented aging as being the most important cause of arterial stiffness, with underlying hypertension as an accelerate of the aging process [[37](#_ENREF_37)]. There is a near twofold increase in aortic pulse wave velocity (PWV) between age 20 and 80. These changes are not nearly as pronounced in the muscular arteries as these vessels are initially less distensible, and experience a more continuous pattern of flow as opposed to the pulsatile flow to which larger central elastic arteries are exposed [[13](#_ENREF_13)]. Fragmentation of the aortic elastic medial lamella can be attributed to the fatiguing effects of pulsatile stress acting over billions of heart cycles [[13](#_ENREF_13)]. PP can be defined as the difference between SBP and diastolic blood pressure (DBP). With aging, there is an

increased PP for a given stroke volume, and this is resultant of increased stiffness and an earlier arrival of the reflective wave, increasing SBP and lowering DBP, which inhibits perfusion, increases myocardial oxygen demand, and causes a mismatch between myocardial demand and supply. An increased resting heart rate likely promotes arterial stiffening through exposing the vessel wall to greater cyclic stress [[38](#_ENREF_38)]. Hypertension accelerates the age associated arterial stiffening process through increasing the stretch of the artery that in turn transfers stress to the less extensible collagenous components of the wall, and renders the stretched artery as stiff [[39](#_ENREF_39)].

**1.1.6*****Non-invasive determination of arterial stiffness***

Regional and local arterial stiffness can be determined directly and non-invasively at various sites along the arterial tree. The measurement of PWV is deemed as the most simple, robust, and reproducible arterial stiffness measurement method, and for those reasons, carotid-femoral PWV has been labeled as the “gold-standard” for determining arterial stiffness [[40](#_ENREF_40)]. Carotid-femoral PWV has been used extensively in epidemiological studies to demonstrate the predictive value of aortic stiffness for cardiovascular events [[40](#_ENREF_40)]. On the contrary, PWV measured outside the central column at the upper (carotid-radial PWV) or lower limb (femoral-tibial PWV) has shown little predictive value for future cardiovascular events [[41](#_ENREF_41)] but still represents a valid assessment of regional stiffness [[42](#_ENREF_42)].

In addition to PWV, arterial stiffness can be assessed through arterial compliance and distensibility as well as augmentation index. Arterial compliance and distensibility may reflect functional changes to the arterial wall that precede structural changes [[43](#_ENREF_43)]. Furthermore, augmentation index, defined as the proportion of central PP due to the late systolic peak, has been shown to be positively correlated with central PWV in clinical populations (r=0.29 p<0.005) [[44](#_ENREF_44)].

**1.1.7*****Measuring PWV***

PWV is routinely measured using the foot-to-foot velocity method from peripheral pressure waveforms [16]. These waveforms are usually obtained at the sites of the right common carotid artery and the right common femoral artery. The foot of the wave is defined at the end of the diastolic phase during the cardiac cycle, when the steep rise of the pressure wavefront begins (Fig. 1). The transit time (Δt) is the time of travel of the foot of the wave over a known distance [[40](#_ENREF_40)]. The time delay between the arrival of the wave from the carotid artery to the femoral artery is measured between the feet of the two waveforms (Fig. 1) [[40](#_ENREF_40)]. Pressure waves can also be recorded from different sites,

**Figure 1. Measurement of carotid-femoral PWV with the foot to foot method.**

and transit time calculated using an electrocardiogram. The distance covered by the waves is identified as the surface distance (*D*) between the two recording sites. It is critical for the distance component used in PWV calculations to be measured precisely as small inaccuracies can obscure the absolute value of PWV [[45](#_ENREF_45)] and the shorter the distance between two sites of interest, the greater the absolute error in determining the transit time. There are various measurement techniques that investigators have historically recommended, including the subtraction of the distance from the carotid location to the sternal notch from the distance between the sternal notch and the femoral site of measurement [[46](#_ENREF_46)]. The distance measurement procedure is unimportant provided that the study is interventional in nature with repeated measures using consistent and reproducible methods. However, when comparing various populations or performing a descriptive or observational study, it is critical that a consistent measuring technique be employed [[40](#_ENREF_40)].

**1.1.8 *Exercise and arterial stiffness***

Studies have shown that both older men and postmenopausal women who performed endurance exercise training demonstrated lower levels of aortic PWV than their sedentary peers [[38](#_ENREF_38), [47](#_ENREF_47)]. However, peripheral arterial stiffness is not different between the sedentary and aerobically active adults [[38](#_ENREF_38), [47](#_ENREF_47)]. As the effects of exercise training were observed only on the central elastic arteries and not the peripheral muscular artery, mechanical or local factors may have interacted with structural or functional mechanisms to improve arterial compliance. When 3 months of endurance exercise were prescribed to postmenopausal women with elevated SBP, only small reductions of aortic PWV occurred, potentially due to the fact that arteries that have been exposed to chronically elevated blood pressure are less susceptible to exercise adaptations.

Compared to adults that are recreationally active, clinically healthy young adult obese men (30 ± 8 yrs) have been shown to have increased aortic cross-sectional area and decreased aortic compliance [[48](#_ENREF_48)]. Previous literature is not consistent with respect to the impact of obesity on arterial stiffness in adults; obese subjects are expected to have a larger stroke volume and cardiac output as a result of a larger body size, and this increased stroke volume could influence arterial compliance. However, in a study conducted by Danias *et al.*, obese adults had elevated SBP which may be the underlying cause for decreased arterial compliance as the chronically elevated blood pressure could change the elastic lamella to more collagenous in nature.

Lack of PA is the second leading behavioural cause of death in the USA, following only tobacco use [[49](#_ENREF_49)] and the aforementioned research has demonstrated some links between increases in PA and decreases in arterial stiffness. Despite these known benefits of PA, recent data have shown that moderate-to-vigorous PA (MVPA) levels decline from childhood to adulthood [[50](#_ENREF_50)], and that sedentary time may also be an important determinant of CVD risk independent of PA [[51](#_ENREF_51), [52](#_ENREF_52)]. A recent study demonstrated that increased sitting time per weekend day, but not per weekday, was positively associated with elevated arterial stiffness, body fat, and resting heart rate in both males and females aged 31.4 ± 3.6 [[53](#_ENREF_53)]. Furthermore, the Canada Fitness Survey [[54](#_ENREF_54)] showed that adults aged 18-90 years had a hazard ratio of 1.54 for both CVD-related and all-cause mortality when greater than ¾ of their time was spent in the sedentary state. CVD-related mortality hazard ratio is nearly doubled when greater than 4h/day is spent watching TV.

**1.1.9*****Arterial compliance and distensibility***

Arterial compliance can be defined as the absolute diameter change for a given pressure change at a controlled length [[55](#_ENREF_55)], while arterial distensibility is the relative diameter change for a given pressure change [[55](#_ENREF_55)]. Total arterial compliance reflects arterial function in the entire systemic circulation while distensibility is an estimate of local arterial elastic properties [[43](#_ENREF_43)]. Both arterial compliance and distensibility are direct measurements of arterial stiffness and may reflect functional changes to the arterial wall that precede structural changes [[43](#_ENREF_43)]. Carotid artery distensibility has been shown to be an independent correlate of mortality whereas carotid arterial compliance is an independent predictor of death or CVD [[43](#_ENREF_43)]. The age-associated changes in arterial compliance have been studied extensively [[56](#_ENREF_56), [57](#_ENREF_57)]. Arterial distensibility of the common carotid artery increases in children, adolescents, and young adults, plateaus near age 30, and begins to decline beyond 30 years of age in those who do not present with risk factors for CVD [[56](#_ENREF_56)].

Throughout the lifespan, engaging in habitual PA has shown to positively influence arterial compliance [[58](#_ENREF_58)]. In young adults, lifetime vigorous PA, not light-to-moderate, is positively associated with arterial compliance [[59](#_ENREF_59)]. In fact, in younger adults, arterial compliance can be increased through PA interventions as brief as one week in duration [59]. These improvements in compliance are, however, likely due to acute residual effects from the preceding exercise bout and not from structural changes to the arteries [[59](#_ENREF_59)]. As arterial changes occur with advancing age [[56](#_ENREF_56)], the acute effects of exercise in young adults are not necessarily similar in older adults. More recently, Nickel and colleagues showed that 30 mins of exercise at 50% of heart rate reserve in adults over the age of 60 (n=32) resulted in transient increases in carotid arterial compliance for up to 30 mins post exercise. This effect was diminished however after the 30 min mark [[60](#_ENREF_60)].

The influence of inflammatory markers on arterial compliance has also been recently documented in young asymptomatic adults. It was discovered that increased levels of c-reactive protein (CRP), an indicator of systemic inflammation, were inversely correlated with large artery compliance [[61](#_ENREF_61)]. However, this relationship was no longer significant after adjusting for age. Whether this response is evident in elderly, clinical, or less-functional patients warrants further investigation. The bioavailability of nitric oxide (NO) may also impact arterial stiffness as studies have shown that NO inhibition results in an increase in aortic PWV that was attributed to increases in blood pressure rather than a specific effect of nitric oxide synthase (NOS) inhibition on the elastic arterial wall [[62](#_ENREF_62)]. In contrast, NOS inhibition did not reduce arterial compliance in a cohort of young adults even though mean arterial pressure and sympathetic vasoconstrictors were elevated [[63](#_ENREF_63)]. It is possible that the lack of change in pulse pressure and the reduced smooth muscle content in the central elastic arteries were linked to the absence of reduced compliance with NOS inhibition in this young healthy population.

**1.1.10*****Measurement of carotid compliance and distensibility***

Compliance of the common carotid artery is often assessed as it is one of the main branches from the aorta and is thus indicative of central elastic stiffness and compliance [[8](#_ENREF_8), [64](#_ENREF_64)]. Direct assessment of common carotid compliance or distensibility can be conducted using combination of B-mode ultrasound imaging and applanation tonometry of the contralateral common carotid artery. Ultrasound images provide a distinct assessment of the change in lumen diameter throughout the cardiac cycle by quantifying the increase in arterial diameter that occurs during systole. The lumen diameter is dependent on the local distending arterial pressure, which is responsible for driving the change in diameter. Assessment of local blood pressure is commonly performed using a hand-held tonometer [[63](#_ENREF_63)] over the point of greatest pulsation of the common carotid artery. Carotid applanation tonometry has been validated against invasive blood pressure measurements, such as the invasive pressure measurement linked to catheterization [[65](#_ENREF_65)].

Day-to-day coefficients of variation for carotid artery diameter are quite low (2 ± 1%) [[63](#_ENREF_63)]. Using several consecutive heart cycles, minimum and maximum carotid artery diameters are determined from the ultrasound images and the following equation is used to calculate distensibility [[55](#_ENREF_55)]:

Where dmax is the maximal lumen diameter, dmin is the minimum diameter, and PP is the carotid pulse pressure. PP is responsible for the change in artery cross sectional area.

**1.1.11*****Vascular endothelium***

Historically, the vascular endothelium was thought to be simply a passive lining of epithelial cells separating the vascular media layer from the flowing blood [[13](#_ENREF_13)]. It has since become apparent that the endothelium produces chemical substances that are designed to maintain homeostasis through elements that act on the intimal surface and on the vascular smooth muscle cells in the media [[66](#_ENREF_66)]. In the endothelium, NO is produced from L-arginine through the activity of the enzyme NOS. Under normal resting conditions, NO is continually released from endothelial cells where it diffuses to the media layer and stimulates relaxation of smooth muscle cells and maintains vascular distensibility. Basal NO mediated vascular smooth muscle relaxation is most active in systemic arteries and less so in resistive arterioles [[13](#_ENREF_13)]. Endothelial shear stress and acetylcholine both stimulate the release of NO from the endothelium [[67](#_ENREF_67)] and the magnitude of shear stress, inversely related to diameter, is commonly presented as systolic (peak), mean, or diastolic stress [[68](#_ENREF_68)]. To avoid errors in shear stress recording, velocity and diameter must be measured at the same location and during the same phase of the cardiac cycle [69].

**1.1.12*****Endothelial function/dysfunction***

Endothelial function is optimal in the young and in those who are disease free and progressive deteriorations are observed with aging. Age-related decreases in endothelial function can be attributed to a thickening of the endothelial layer that is a result of endothelial cell hyperplasia and thickening of the lamina membrane that separates the intimal layer from the medial layer. Decreases in endothelial function may also be related to the degradation of the gaseous NO when required to travel a greater distance before reaching its activation site in the vascular smooth muscle [[13](#_ENREF_13)]. These pathological processes are further expressed in atherosclerosis, when the distance between the endothelium and medial site is further increased by the deposition of atherosclerotic plaques.

Endothelial dysfunction is prevalent in persons with risk factors for atherosclerosis, including hypertension, hypercholesterolemia, and obesity [[66](#_ENREF_66), [70](#_ENREF_70)]. Impaired endothelial function is evident prior to the appearance of coronary atherosclerosis and has therefore been suggested as a valuable tool for early detection of CVD. Endothelial dysfunction is linked to the pathophysiology of atherosclerosis through the promotion of the adherence of monocytes and lipoproteins to the arterial wall, entry into the wall, and the inflammatory response and subsequent lipid deposition. Furthermore, studies have confirmed a distinct correlation between measurements of peripheral vascular endothelial dysfunction in the brachial artery and coronary atherosclerosis [[66](#_ENREF_66), [71](#_ENREF_71)].

**1.1.13*****Measurement of endothelial function – flow-mediated vasodilation***

The flow-mediated vasodilation (FMD) assessment was originally introduced by Celermajer *et al.* in 1992. It has now become the most widely used method to measure endothelial function in humans. This technique requires the dual recording of brachial arterial diameter and blood velocity at baseline and during reactive hyperemia. To establish a flow stimulus in the brachial artery, a blood pressure cuff is placed distal to the antecubital fossa, and is inflated to at least 50 mmHg above systolic pressure to occlude arterial inflow for a standardized length of time, usually 5 minutes [[72](#_ENREF_72)]. Prior to cuff inflation, a baseline rest image and velocity signal are recorded using Duplex mode ultrasonography [[72](#_ENREF_72)]. Thereafter, arterial occlusion is created by cuff inflation to a supra-systolic pressure that results in ischemia and consequent dilation of downstream resistance vessels. After a 5 minute occlusion period, subsequent cuff deflation results in a brief high-flow state (reactive hyperemia) to provide blood to the dilated vessels. The resulting increase in shear stress in the conduit artery (brachial) supplying the ischemic downstream tissue causes the brachial artery to dilate [[73](#_ENREF_73)]. Provided that a positive linear relationship exists between relative FMD and shear rate, normalization of the data is possible [[67](#_ENREF_67)]. Normalization facilitates comparison of endothelial dependent FMD responses between groups differing in baseline diameter. Furthermore, it is important to adhere to statistical assumptions when normalizing FMD. If the relationship between shear rate and FMD is weak then normalization should not be applied. When normalized, the FMD/shear rate ratio has been used to distinguish reduced endothelial function in a population with moderate risk for CVD from that of low risk [[74](#_ENREF_74)]. Regardless, the FMD measurement technique and resulting values need to be standardized before the method becomes a part of routine clinical evaluation of CVD risk [[75](#_ENREF_75)].

**1.1.14*****Endothelial function and exercise***

There is an inverse relationship between the level of PA and cardiovascular events [[76](#_ENREF_76)]. Improved endothelial function that is seen with exercise is due to increased expression of the enzyme NOS in response to increased endothelial shear stress as a result of increased blood flow that occurs during exercise [[77](#_ENREF_77)]. Consistent with this, previously sedentary middle (27 ± 1 yrs) and older (58 ± 2 yrs) aged men completing a 3-month at home exercise intervention increased endothelium dependent dilation by 30% [[78](#_ENREF_78)]. In young healthy men (mean 20 yrs), 10 weeks of combined aerobic and anaerobic exercise training increased endothelial dependent dilation by 77% [[79](#_ENREF_79)]. Contrary to this, brachial artery FMD was not changed when recreationally active young adults were instructed to reduce PA for 5 days [[80](#_ENREF_80)] suggesting that previously active individuals can maintain endothelial function in the face of a brief period of reduced activity. Therefore the literature suggests that PA does have a beneficial role in both increasing and maintaining endothelial function in young, middle and older aged healthy men. Similarly, it was shown that 4 weeks of PA improved endothelial function in patients with coronary artery disease through the enzyme NOS [[81](#_ENREF_81)]. In contrast, PA in healthy children restores seasonal decreases in endothelial function to normative values but does not increase above those levels [[82](#_ENREF_82)]. Thus it seems that increasing PA enhances endothelial function in young, middle, older, and in individuals with increased CVD risk.

**1.2** **OTHER CVD RISK FACTORS**

**1.2.1*****Physical activity***

The accurate assessment of PA is essential when examining the association between PA and health related outcomes. Self reports of PA are susceptible to inaccuracy as they rely on an individual’s ability to recall on previous activities [[83](#_ENREF_83)]. The development of devices for the measurement of PA has allowed researchers to more accurately measure the entire range of activity, from sedentary to very vigorous behavior, over a number of days. Accelerometry has been validated as an objective method of assessing PA, and has become a highly reproducible measure for quantifying PA [[84](#_ENREF_84)]. Accelerometers are devices that measure body movement in the form of acceleration which can then be used to estimate intensity of activity over a given time period [[85](#_ENREF_85)]. Most accelerometers house one, or multiple, piezoelectric elements, and during acceleration, a seismic mass causes the element to experience deformation, which is recorded as a voltage and digitized to counts. Counts are then binned into select time periods, or epochs, to represent the count for that time period [[85](#_ENREF_85)]. Choosing a short epoch is important if PA is sporadic and is accumulated in multiple short bouts. However, a disadvantage with shorter epochs is that their predictive physiological value in terms of risk reduction is relatively unknown. On the contrary, the main drawback of using a longer epoch is if a bout contains a mixture of activities at varying intensities, then the data will be averaged to reflect mean intensity. Initial observational studies in adults without diabetes (mean age 53.4) equipped with accelerometers have shown that device-measured increases in sedentary time is directly associated with elevations in a number of CV risk factors, specifically waist circumference (WC), blood glucose, insulin, and triglycerides [[86](#_ENREF_86)]. These results have also been shown to be independent of MVPA levels. An interesting finding from this study was that adults who interrupted their sedentary bouts with more frequent ‘breaks’ had a better cardiovascular profile than those who endured in longer periods of sedentary time [[86](#_ENREF_86)]. Interruptions in sedentary time being a transition from sedentary (<100 counts per minute (CPM)) to an active state (>100CPM) were deemed a ‘break’. The number of breaks was summed over valid days. The benefits of taking breaks were independent of time spent in MVPA. When looking at differences between breaks in sedentary time, the most significant findings were observed for WC. Of the 25% that took the most breaks, they had a 4.1cm smaller WC compared to the lowest group [[86](#_ENREF_86)].

**1.2.2*****Insulin***

Insulin is a hormone that is produced by beta cells in the pancreas that influences the absorption of glucose by skeletal muscle and fat tissue cells from the blood [[87](#_ENREF_87)]. Increased levels of circulating insulin prevent the usage of triglycerides as an energy source by inhibiting the release of glucagon [[87](#_ENREF_87)].

Insulin resistance and hyperinsulinemia enhance alterations that can lead to the progression of atherosclerosis [[88](#_ENREF_88)]. Insulin also exhibits a protective effect on the vascular smooth muscle as insulin has been shown to stimulate endothelial cell production of NO [[89](#_ENREF_89)] through the phosphatidylinositol 3-kinase pathway [[87](#_ENREF_87)]. On the contrary, hyperinsulinemia promotes the effect of platelet-derived growth factor and other growth factors on vascular smooth muscle cells [63]. In this detrimental pathway, insulin acts through the mitogen-activated protein kinase pathway to indirectly produce vascular smooth muscle cell growth and plasminogen activator inhibitor-1; which attenuates fibrinolysis [[90](#_ENREF_90)] and subsequently results in the progression of arterial stiffness [[91](#_ENREF_91)]. Insulin also enhances cholesterol transport into arterial smooth muscle cells and increases lipid synthesis of these cells. Elevated plasma insulin concentrations enhance very-low-density lipoprotein synthesis. Progressive elimination of lipids from the very-low-density lipoprotein particle leads to an increased formation of low-density lipoprotein (LDL) in the arterial medial layer and increases endogenous lipid synthesis by these cells [[92](#_ENREF_92)].

Recently, studies have focused on the effects of weight loss, reduced WC, and insulin reduction in adults and youth to determine the effects on arterial stiffness [[93-96](#_ENREF_93)]. Body mass index (BMI) and WC were found to be correlated with each other and with steady-state plasma glucose concentrations in 330 non-diabetic adults. The more overweight or obese a person, the greater the degree of insulin resistance, which was independent of either index of adiposity (BMI or WC) [[96](#_ENREF_96)]. Weight loss [[97](#_ENREF_97)] and improved insulin sensitivity have been shown to be independently associated with improved aortic stiffness [[98](#_ENREF_98)] but combined effects of weight loss and increased insulin sensitivity on aortic arterial stiffness have been poorly understood. In a large cohort of healthy men and women (n=339), with an average age of 37.9 years, decreases in brachial-ankle PWV were associated with reductions in weight and insulin levels that were independent of age, sex, race, smoking, status, and brachial blood pressure, following a 6 month interventional trial [[93](#_ENREF_93)]. Changes in stiffness were only observed in brachial-ankle PWV and not in central PWV. In healthy adolescents and young adults, mean age 20.8 ± 2.6, traditional cardiovascular risk factors such as age, BMI, and blood pressure were the most consistent determinants, while HOMA-IR was not an independent determinant of arterial stiffness [[94](#_ENREF_94)]. However, results confirmed that a more adverse cardiovascular risk profile and stiffer arteries were found in young obese individuals presenting with insulin resistance.

It has been suggested that a sex difference may exist with regards to insulin sensitivity. The female advantage in CVD risk refers to the approximately 10-year delay in the incidence of CVD in women compared with men [[99](#_ENREF_99)]. Kim *et al.* examined whether a sex difference in insulin resistance might explain this 10-year advantage for women in a group of younger adults (<51; mean 40.1; 244 women, 147 men) and older adults (>51; mean 58.9; 224 women, 207 men). Steady-state plasma glucose concentration, a direct measure of the ability of insulin to mediate glucose disposal, was not different between the sexes in either age group. However, when the groups were separated into tertiles, women had lower CVD risk in the most insulin resistant tertile as displayed in lower LDL, triglyceride, and fasting glucose levels [[100](#_ENREF_100)].

***1.2.3******Glucose***

In the postprandial state, skeletal muscle is the primary tissue responsible for insulin-dependent overall body glucose uptake [[101](#_ENREF_101)] and becomes a source of metabolic fuel during the commencement of exercise. However, in elevated glucose states, also referred to as hyperglycemia, glucose has been shown to be associated with arterial stiffening [[102](#_ENREF_102)] through the formation of advanced glycation end products in the arterial wall. Chronic hyperglycemia enhances the reaction between glucose and proteins and aids in the cross-linking of collagen. Hyperglycemia has further been shown to promote collagen deposition and tissue inflammation within the smooth muscle cells of the vasculature [[103](#_ENREF_103)].

Recently, researchers have shown that chronic hyperglycemia (as assessed using HbA1c) is strongly correlated with arterial stiffness independent of the artery wall thickness [[102](#_ENREF_102)] in 9050 adults with a mean age of 56.7 years. Furthermore, a 25% increase in fasting glucose levels in men aged 45 to 64 years was associated with a 5.8% decrease in arterial compliance and a 5.8% increase in stiffness [[104](#_ENREF_104)]. Finally, when comparing individuals with type-2 diabetes to those with impaired glucose metabolism and normal glucose metabolism, independent of age, sex and mean arterial pressure, researchers found that those with type-2 diabetes had increased arterial stiffness of carotid, femoral, and brachial arteries whereas those with impaired glucose metabolism had increased stiffness of the muscular arteries only [[105](#_ENREF_105)]. These findings suggest that the process of increasing arterial stiffness occurs prior to the onset of occult type-2 diabetes. Increases in fasting plasma glucose, even within normal ranges (<100mg/dL), have been associated with increased brachial-ankle PWV in 697 healthy adults without diabetes with an average age of 51.9 years [[106](#_ENREF_106)]. Although the aforementioned studies adjusted for age in their analyses, the average age of participants was approximately 50 years. When glucose intolerance and insulin resistance were examined in children, arterial stiffness examined using PWV was significantly higher in those with impaired glucose control. This relationship was, however, dependent on blood pressure, BMI, and intraventricular septal thickness [[107](#_ENREF_107)], thus it seems that hyperglycemia is an independent predictor of arterial stiffening in older, but not younger individuals.

**1.2.4 *Interleukin-6***

Interleukin (IL)-6 is a cytokine with a broad range of humoral and immune effects relating to inflammation, bacterial defense, and tissue injury [[108](#_ENREF_108)]. IL-6 is produced in response to several factors, including infection, elevations in IL-1 and -2, and tumor necrosis factor [[109](#_ENREF_109)]. IL-6 is also a primary determinant of the production of CRP from the liver [[110](#_ENREF_110)].

Elevated levels of IL-6 have been linked to the inflammatory processes that lead to atherosclerosis [84]. IL-6 can activate endothelial cells to express adhesion molecules, which mediate trans-endothelial migration of leukocytes resulting in fatty streaks and the formation of atherosclerotic plaques [[111](#_ENREF_111)]. Furthermore, IL-6 is produced in the adipose tissue in response to adipocytokines linking obesity to the state of chronic low-level inflammation as a potential trigger for cardiovascular and metabolic diseases [[112](#_ENREF_112)]. IL-6 is involved in the migration and proliferation of smooth muscle cells [[113](#_ENREF_113)]. The progression of atherosclerosis in the presence of increased circulating levels of IL-6 has been linked to central arterial aging as a result of endothelial dysfunction and arterial stiffening [[114](#_ENREF_114), [115](#_ENREF_115)]. As atherosclerosis is an inflammatory disease, the inflammatory response of the endothelium disrupts its membranous integrity and allows an influx of LDL and monocytes [[116](#_ENREF_116)]. LDL, upon oxidative or enzymatic modification, further promotes the inflammatory reaction in the evolving atherosclerotic plaque. Prolonged inflammation stimulates migration and proliferation of smooth muscle cells, which along with the accumulating macrophages, further release cytokines and growth factors [[116](#_ENREF_116)]. These processes result in a destructive remodeling of the vessel structure with the formation of a complex atherosclerotic lesion [[117](#_ENREF_117)]. The presence of IL-6 and the associated relationship with endothelial dysfunction and arterial stiffness have been shown to be independent of other cardiovascular risk factors (blood pressure, low levels of high-density lipoprotein (HDL), fasting plasma glucose, WC, and serum triglycerides) [[115](#_ENREF_115)].

**1.2.5 *Lipids***

HDL is a plasma lipoprotein that aids in reverse cholesterol transport, bringing cholesterol from peripheral cells to the hepatic system, where cholesterol is subsequently secreted into the bile [[118](#_ENREF_118)]. HDL formation begins as a result of the liver and small intestine secreting apolipoprotein A-I. Apolipoprotein A-I circulates in the plasma acquiring cholesterol from peripheral cells [[119](#_ENREF_119)]. HDL levels have been shown to be inversely associated with coronary heart disease and for a 1% increase in HDL levels, coronary events decrease by approximately 2% [[120](#_ENREF_120)]. The major cardiovascular benefit of HDL is attributed to its role in transferring cholesterol, specifically LDL, from macrophages in atherosclerotic lesions to the liver [91]. HDL has also been shown to improve vascular function through the activation of endothelial NOS [[121](#_ENREF_121)]. In persons with familial hypoalphalipoproteinemia, resulting in low-HDL levels, endothelial dysfunction is present [95]. Researchers found that by administering apolipoprotien A-I to 3 men and 6 women (42.9 ± 13.9 yrs) with familial hypoalphalipoproteinemia, previous blunted blood flow responses were returned to levels similar to healthy controls when challenged with a vasodilator (serotonin) [[122](#_ENREF_122)]. HDL has also been shown to inhibit vascular inflammation by decreasing the expression of E-selectin [[123](#_ENREF_123)] and adhesion molecules such as vascular cell adhesion molecule [[124](#_ENREF_124)]. Vascular inflammation begins when LDL is deposited into the arterial wall, resulting in endothelial cells to express selectins and adhesion molecules. This expression leads to leukocyte infiltration within the arterial wall, and oxidization of LDL macrophages into inflammatory foam cells, resulting in atherosclerosis [[125](#_ENREF_125)].

By activating endothelial NOS, HDL can increase levels of NO, which can inhibit platelet aggregation [[119](#_ENREF_119)]. Research has shown that HDL infused intravenously in adults aged 57 ± 9 yrs with hypercholesterolemia (LDL levels >4.0mmol/L) significantly increased brachial artery FMD and acetylcholine induced vasodilation [99]. Thus, in adults with hypercholesterolemia who are at risk of atherosclerosis, increasing levels of HDL may attenuate progression of atherosclerosis through removal of LDL depositions from the vascular wall [[126](#_ENREF_126)].

LDL is a plasma lipoprotein that promotes fatty deposition in the intimal layer of the vasculature, leading to leukocyte adhesion and macrophage infiltration, ultimately resulting in foam cells and plaque accumulation [[119](#_ENREF_119)]. Plaque accumulation is the underlying cause of atherosclerosis and arterial stiffening. LDL has also been shown to stimulate collagen synthesis in arterial smooth muscle cells [[127](#_ENREF_127)], promotes intimal thickening, and impairs NO bioactivity [[128](#_ENREF_128)]. From data derived in the Health, Aging and Body Composition (Health ABC) Study, it was determined that oxidated LDL levels were associated with increased arterial stiffness independent of traditional cardiovascular risk factors such as PA levels, blood pressure, and HDL cholesterol levels [102]. These risks were further exacerbated in those with LDL levels greater than 144 ± 33 mg/dL, in which they were at a 30-55% increased risk of having high arterial stiffness (>10.54m/s) [[129](#_ENREF_129)]. In a sample of young females, aged 18 to 30 years, those with dyslipidemia had significantly impaired endothelial function which was correlated with increased muscle sympathetic nervous system activity and elevated inflammatory markers [[130](#_ENREF_130)].

**1.3 CEREBRAL PALSY**

CP is a cause of disability that impacts a person across their lifespan [[9](#_ENREF_9)]. CP has a prevalence of 1.7 to 2.3 per 1000 live births [[131](#_ENREF_131), [132](#_ENREF_132)]. CP is a heterogeneous disorder that displays itself in numerous physiologic, neurologic, musculoskeletal, and psychosocial ways. Physiologic descriptors of CP are spastic, ataxic, dyskinetic, and mixed [[133](#_ENREF_133)]. Bax originally defined CP in 1964 as a group of disorders in the development of posture and motor control, occurring as a result of a non-progressive lesion of the developing central nervous system [[134](#_ENREF_134)]. This definition was later expanded and revised to encompass the secondary impairments that accompany CP:

*Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disturbances of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems.* [[135](#_ENREF_135)]

A five-level classification system was developed to classify the gross motor function, or control, of children with CP [[136](#_ENREF_136)]. This system, known as the Gross Motor Function Classification System (GMFCS), was derived to enhance communication among professionals and families with respect to determining a child’s needs, describing the development of children with CP, and generalizing the results of research into the outcome of treatment [[137](#_ENREF_137)]. The GMFCS reports the major functional characteristics of children with CP in each level within several age groups: birth to age 2, between ages 2 and 4, between ages 4 and 6, and between ages 6 and 12 years. Motor curves have been developed on the grounds of the five levels of function, demonstrating that individuals’ motor function generally remain stable over time [[138](#_ENREF_138)]. Studies have reported good to excellent inter-rater reliability for the severity of gross motor function limitations using the GMFCS in children with CP [[137](#_ENREF_137), [139](#_ENREF_139)]. With respects to topographic distribution in children, Gorter *et al.* reported that those with hemi- and diplegia were most represented in GMFCS levels I, II and III, whereas those with tri- and quadriplegia were represented in GMFCS levels IV and V. Furthermore, with respect to type of motor impairments, 78% of the cohort was spastic and 33% of the spastic individuals were in GMFCS level I [[140](#_ENREF_140)]. The relationship between limb distribution and GMFCS levels was stronger when two categories of limb distribution were used as opposed to four. Finally, the prevalence of CP recognizing motor function level is greatest in GMFCS level I (1.3/1000). Whereas levels II-V averaged 0.3/1000 births [[141](#_ENREF_141)].

Although CP is a condition that spans a lifetime, there is no defined systematic follow-up of adults with CP after the age of 18, and the literature is limited with regards to studies that have used the GMFCS in adults [[142](#_ENREF_142)]. The intraclass correlation coefficient between professional rating and self-reported GMFCS levels is high (0.93) [[138](#_ENREF_138)]. With regards to stability in GMFCS level as children with CP progress into their adult years, in a cohort of 62 adults with CP, 52% did not show any changes, whereas 40% showed a change in classification to a lower level of function in comparison to when they were 10 to 12 years [[138](#_ENREF_138)]. The majority of participants described pain, exhaustion, and balance problems as the underlying reason to choose a wheelchair as the main mode of transportation, thus transposing them into a lower functioning level [124]. Therefore, based on the intraclass correlation coefficient, the GMFCS seems to be a strong tool for identifying the level of motor function in adults with CP.

**1.3.1*****Cerebral palsy and physical activity***

The majority of studies that have examined PA levels in the CP population have done so in cohorts of children [[143-147](#_ENREF_143)]. PA levels and total energy expenditure have both been shown to be lower in children with CP who have moderate to high gross motor function compared to their typically developing peers [[115-118](#_ENREF_115)]. Furthermore, PA levels of adolescents with CP were related to level of GMFCS and were inversely related to age [[146](#_ENREF_146)]. What may be particularly interesting was that sedentary activity patterns, such as TV and computer use, in adolescents with and without CP were similar. Thus, typically developing children engage in more PA but sedentary times are not different from higher functioning peers with CP [[146](#_ENREF_146)]. Although total energy expenditure is similar between higher functioning children with CP and typically developing peers, the energy expenditure associated with walking is greater in children with CP that have lower PA levels [[148](#_ENREF_148)]. Ambulatory children with CP also have higher mean heart rate values at rest compared to their typically developing peers [[145](#_ENREF_145)], while vigorous activity levels in ambulatory children with CP were lower than their typically developing peers. Despite these differences in activity levels, several indexes of vascular structure and function measures were not different between higher functioning adolescents with CP and their age matched healthy peers [[149](#_ENREF_149)]. These relationships have yet to be examined in the adult CP population.

Although PA data in adults with CP is scarce, relationships similar to those observed in children with CP exist [[150](#_ENREF_150)]. Young adults with CP having moderate to high gross motor function ability participated in up to 53% less PA than their peers, and these levels were 30% less than guidelines [[144](#_ENREF_144)]. Furthermore, sedentary times in these young adults with CP were twice the maximum recommended amount, therefore making this population at an increased risk for CVD [130]. Similar to children with CP, it has been shown that adults with CP who are able to walk without assistive devices, younger in age, and have positive perceptions of health are more likely to be active [[151](#_ENREF_151)]. Physical strain also limits walking ability in adults with CP. Adults with CP with high physical strain, identified as the oxygen uptake while walking as a percentage of peak aerobic capacity, are likely to walk less in daily life [[152](#_ENREF_152)]. This would imply that as gross motor function decreases, persons with CP would have lower walking/activity times, but greater energy expenditure during walking.

Regardless of age, persons with CP are at an increased risk for increased levels of inactivity and low fitness, which can lead to secondary health complications. One exception to this trend has been noted, however, in that levels of daily PA in adults with CP that are high functioning are comparable to levels in healthy subjects. It should be emphasized that this study was conducted in a small cohort (n=16) with highest levels of motor functioning [[153](#_ENREF_153)]. Persons with CP are also likely not to receive structural treatment to improve fitness and activity levels in their late adolescent years, which is precisely the period when adult PA patterns are developed [[154](#_ENREF_154)]. This is particularly important in Ontario, Canada, where government funded coverage for physio- and occupational therapy terminates at age 18 [[155](#_ENREF_155)]. The most recent literature has suggested that simply striving for increases in MVPA may not be enough. It may be of greater importance to replace sedentary behavior with light PA in adults with CP to put them at a lower risk for developing secondary complications, such as CVD [[156](#_ENREF_156)].

**1.3.2*****Secondary complications in adults with cerebral palsy***

Persons having a disability are at an increased risk of inactivity [[157](#_ENREF_157)]. For adults with CP, impaired function and poor health typically present common barriers to participation in PA. Adults with CP are likely not engaging in sufficient PA to produce the improvements in fitness required to experience positive health benefits [[10](#_ENREF_10)]. The most commonly reported age-related changes and secondary conditions in adults with CP involve pain and fatigue, physical performance, and changes in the musculoskeletal system [[158](#_ENREF_158)], such as joint deformities of the legs and scoliosis [[159](#_ENREF_159)].

In studies examining the long-term survival and life expectancy of adults with CP [[11](#_ENREF_11), [160](#_ENREF_160)], those having the highest functioning levels with CP had a life expectancy that was only 5 years less than the normal population. Life expectancy becomes much more variable as the severity of CP increases [[160](#_ENREF_160)]. With respect to cause of death, many more deaths have been attributed to diseases of the respiratory and circulatory system in adults with CP aged 20-50, compared to the general population, and these are typically more pronounced in the more severely affected [[11](#_ENREF_11)].

Gaps in the literature are clearly evident with respect to respiratory and cardiovascular changes as persons with CP progress from adolescence into adulthood. Prior studies have focused on capturing the changes, if any, in gross motor function during this time frame [[161-165](#_ENREF_161)]. There seems to be a clear consensus that in those who are highest functioning in childhood are the ones that retain this ability throughout adulthood [[161](#_ENREF_161), [162](#_ENREF_162), [165](#_ENREF_165)]. What is even more interesting is that those who ambulate with difficulty at age 10 have a chance to improve through adolescence, whereas those with poorer function and/or using a wheelchair likely decline [[162](#_ENREF_162)]. In children, the ‘stable-limit’ model was adapted for those in GMFCS levels I and II, stating that motor development is accelerated up to age 5, and remains stable afterwards. The ‘peak and decline’ model showed a peak in development at age 7, which began to decline afterwards, and was highlighted in GMFCS level IV [[165](#_ENREF_165)]. Studies have shown that in the adult population, a third had deteriorated in motor function from adolescence to adulthood and this trend was evident in lower functioning individuals during their younger years [[142](#_ENREF_142)]. Loss of motor function with aging in CP has been associated with weight increases [[161](#_ENREF_161)] and a reduction in contact with rehabilitation services [[163](#_ENREF_163), [166](#_ENREF_166)].

While the specific mechanisms of secondary complications in adults with CP are not well defined, evidence exists to suggest that individuals with CP have lower fitness [[152](#_ENREF_152)] and reduced functional reserve throughout adulthood [[167](#_ENREF_167)]. Along with the motor impairments evident in adults with CP, high rates of sedentary time and diminished fitness have resulted in a comparison to individuals with a spinal cord injury [[168](#_ENREF_168)]; a population with enhanced sarcopenia, increased adiposity, insulin resistance, hyperlipidemia and CVD risk. However, in comparison to most traumatic SCI, individuals with CP have the added risk of muscle deterioration and metabolic dysregulation from birth.

Mortality records have shown a nearly threefold greater death rate from coronary artery disease in adults with CP compared to the general population [[169](#_ENREF_169)]. Most of the research conducted has been observational and cross-sectional in nature, thus unable to track changes over time in outcome variables such as obesity, metabolic dysregulation, and CVD. The majority of these studies have looked at energy expenditure [[170](#_ENREF_170)], simple anthropometric measures [[171](#_ENREF_171)], and cardiometabolic markers [[172](#_ENREF_172)], which limit the predictability of risk over time. Studies have shown that adults with CP with lower gross motor function have an increased resting metabolic rate compared to those who are higher functioning [[173](#_ENREF_173)], however total energy expenditure is greater in those who are ambulatory [[167](#_ENREF_167)]. These elevations in resting metabolic rate in non-ambulatory individuals with CP are unlikely sufficient to attenuate negative health impairments associated with their low activity levels and high sedentary behaviours. A recent study showed that increased sedentary behavior was associated with increased adiposity and intermuscular adipose tissue [[174](#_ENREF_174)]. Individuals with lower gross motor functioning, particularly GMFCS levels IV and V, have lower BMI compared to higher functioning individuals (GMFCS I-III) [[172](#_ENREF_172)] while dual-energy x-ray absorptiometry measures indicate that those less functioning actually had greater adipose tissue, and increased TC/HDL-C ratio [[172](#_ENREF_172)]. These conflicting anthropometric results indicate that BMI is likely not a valid predictor of cardiometabolic risk in the adult CP population. In support of this theory, it has been recently shown that higher body fat was the strongest predictor of 10-year CVD risk in a cohort of adults with CP [[175](#_ENREF_175)].

**1.3.3 *Physical activity and cardiovascular health in adulthood***

CP is a permanent disability that limits activity across the lifespan [115]. It has been identified that PA levels of persons with CP are related to the level of gross motor function and are inversely associated with age [131], thus potentially placing adults with CP who are lower functioning at an increased risk of CVD. The potential consequences of this reduced activity on specific parameters of arterial health and CVD risk in an adult population of CP patients have yet to be examined. To our knowledge, there is no previous published assessment of the potential impacts of this physical disability on levels of PA and vascular health in adults with CP.

**1.4 PURPOSE AND HYPOTHESIS**

The purposes of this study were to provide normative assessments of arterial structure (cIMT) and function (FMD, PWV, and carotid distensibility) and PA patterns in adults aged 18-75 with GMFCS levels I-V CP to determine if inactivity is predictive of compromised vascular health.

We hypothesize that adults with CP who are of higher functioning (GMFCS I-II) will have increased levels of PA, increased endothelial function (FMD) and decreased arterial stiffness (distensibility and PWV) compared to those who are lower functioning (GMFCS III-V).

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**CHAPTER 2**

RELATIONSHIPS BETWEEN MOTOR CLASSIFICATION, PHYSICAL ACTIVITY AND CARDIOVASCULAR HEALTH IN ADULTS WITH CEREBRAL PALSY

**2.1 INTRODUCTION**

Cerebral palsy (CP) is a disability that impacts a person throughout their lifespan [[1](#_ENREF_1)] and limits activity as a result of disturbances that occurred during the development of the fetal or infant brain [[2](#_ENREF_2)]. Despite the lifelong implications, there is no defined systematic follow-up of adults with CP after the age of 18 [[3](#_ENREF_3)]. The Gross Motor Function Classification System (GMFCS) is a five-level classification system that was developed to classify gross motor function of children with CP [[4](#_ENREF_4)]. This scale has been adopted by the adult population, and studies have shown that 40% of adults with CP are in a lower GMFCS level compared to when they were children [[5](#_ENREF_5)]. Reasons behind this decline in motor function may include the long-term impacts of pain, exhaustion, and balance problems. As such, adults with CP are less physically active than their healthy aged counterparts [[6](#_ENREF_6), [7](#_ENREF_7)].

Lack of physical activity (PA) is the second leading behavioural cause of death in the USA, following only tobacco use [[8](#_ENREF_8)]. Lifelong decreases in PA could put adults with CP at an elevated risk of developing a variety of secondary complications, including cardiovascular disease (CVD) [[9](#_ENREF_9)]. It has been identified that PA levels of individuals with CP are related to the level of GMFCS and are inversely associated with age [[10](#_ENREF_10)]. Furthermore, young adults with CP with moderate to high gross motor function typically participate in less than half the amount of PA of their able-bodied peers [[6](#_ENREF_6)].

Healthy adults over the age of 18 have been shown to be at an increased risk of CVD-related and all-cause mortality when greater than 75% of time is spent in the sedentary state [[11](#_ENREF_11)]. Sedentary time has been identified as being detrimentally associated with higher waist circumference (WC), hyperglycemia, and hyperinsulinemia [[12](#_ENREF_12)]. Sedentary times in adults with CP have been reported to be twice the maximum recommended amount, therefore suggesting that this population may be at an increased risk for CVD [[6](#_ENREF_6)]. One reason for reductions in PA and elevations in sedentary time in adults with CP may be the fact that individuals with CP are less likely to receive structured treatment to improve activity patterns in their late adolescent years, which is the period when adult PA patterns are developed [[13](#_ENREF_13)]. The potential consequences of this sedentary lifestyle on emerging CVD risk factors of arterial health and biomarkers of inflammation and metabolism in an adult population of individuals with CP have yet to be examined. Although some limited literature does exist on causes of mortality [[31](#_ENREF_31)], predictors of cardiometabolic risk [[32](#_ENREF_32)], and coronary risk evaluation in the adult CP population [[33](#_ENREF_33)], to our knowledge, there is no assessment of the potential impacts of this physical disability on levels of PA, vascular and cardiometabolic health in adults with CP. Comprehensive assessment of traditional and novel CVD risk factors in adults with CP may help in the early detection of CVD and in the evaluation of interventions designed to combat CVD.

It has been suggested in healthy populations that engaging in PA can increase elastin content and attenuate the progression of collagen within the arterial wall, thereby slowing the age-associated increase in arterial stiffness [[14](#_ENREF_14)]. Pulse wave velocity (PWV) is a robust and reproducible measure of arterial stiffness with increases in PWV being a subsequent marker of CVD risk [[15](#_ENREF_15)]. In adults, obesity, age, hypertension, hyperinsulinemia, and hyperglycemia have been shown to positively correlate with PWV, while increased levels of PA present with a negative relationship [[16](#_ENREF_16)]. Carotid intima media thickness (cIMT) and distensibility are two additional indices of arterial health that assess structure and function, respectively. A cIMT greater than 0.82mm has been shown to increase the risk of myocardial infarction, stroke, and peripheral arterial disease in middle-aged men [[17](#_ENREF_17)]. The impact of PA on IMT has been controversial, with exercise training interventions longer than 3 months in duration required to elicit positive changes [[18](#_ENREF_18)]. Increases in IMT and reductions in distensibility have also been observed in adults with CVD risk factors such as dyslipidemia [[19](#_ENREF_19)], inflammation [[20](#_ENREF_20)], and obesity [[21](#_ENREF_21)].

PA has also been shown to exhibit positive effects on the vascular endothelium as a result of elevated shear stress caused by increased blood flow that occurs during exercise [[22](#_ENREF_22)]. Endothelial dysfunction is present in individuals with risk factors for atherosclerosis, including those with hypertension, hypercholesterolemia, and obesity [[23](#_ENREF_23), [24](#_ENREF_24)]. Impaired endothelial function is considered a precursor to coronary atherosclerosis [19]. Endothelial function is optimal in the young, and there is a progressive deterioration with aging [[25](#_ENREF_25)]. Endothelial function is therefore an indicator of pre-clinical vascular disease and for adults with CP, may act as a signal for early changes in arterial function.

The accumulation of certain metabolic markers has been shown to enhance CVD risk. Particularly, insulin resistance and hyperinsulinemia enhance alterations in the vasculature that can lead to the progression of atherosclerosis [[26](#_ENREF_26)]. Hyperglycemia has been associated with arterial stiffening through advanced glycation end products [[27](#_ENREF_27)]. Similarly, low-density lipoprotein (LDL) results in foam cell production and plaque accumulation – the underlying cause of atherosclerosis and arterial stiffening [[28](#_ENREF_28)]. On the contrary, high-density lipoprotein (HDL) levels have been shown to be inversely associated with coronary heart disease. Increased levels of the inflammatory marker interleukin (IL)-6 have been involved in the migration and proliferation of smooth muscle cells [[29](#_ENREF_29)] leading to the formation of atherosclerotic plaques [[30](#_ENREF_30)].

The purpose of this study was to examine relationships between GMFCS levels, PA, arterial structure (cIMT) and function (flow-mediated dilation (FMD), PWV, and carotid distensibility) and cardiometabolic risk markers (lipids, glucose, IL-6) in adults aged 18-75 with GMFCS levels I-V CP to determine if inactivity is predictive of compromising vascular health. We hypothesized that adults with CP who are community ambulatory (GMFCS I-II) will have increased levels of PA, increased endothelial function, decreased arterial stiffness and decreased cardiometabolic risk compared to those who are non ambulatory (GMFCS III-V).

**2.2 METHODS**

**2.2.1 *Participants***

Forty adults with CP (mean age 33.7 ± 12.7 yrs) were recruited from across Ontario. Inclusion criteria consisted of a GMFCS [[34](#_ENREF_34)] level I-V, regardless of intellectual ability. All CP subjects were identified and segregated using the GMFCS (level I n=5, level II n=9, level III n=10, level IV n=9, level V n=7). The Hamilton Integrated Research Ethics Board granted study approval. Experimental procedures were thoroughly explained to participants and/or their guardians prior to obtaining written consent.

**2.2.2 *Study design***

This study employed a cross-sectional, observational design to characterize the specific measures of vascular structure and function, PA levels and blood markers specific to insulin, glucose, lipid panel (cholesterol), and inflammation. The eight-day study protocol required a single visit to the Vascular Dynamics Laboratory at McMaster University. On day one, a waist and wrist accelerometer with an accompanying logbook to record wear times were delivered personally or via courier to the participant’s place of residence. Participants were instructed to wear the accelerometer for seven consecutive days. On the eighth day the participants arrived at the Vascular Dynamics Laboratory and were assessed for basic anthropometry and vascular indices, and a blood sample was obtained. Vascular measures were collected in a quiet, temperature-controlled room (23.2 ± .9oC) with the participant in a supine position. All subjects were tested at least 12 hours postprandial. Subjects were also instructed to abstain from vigorous PA at least 12 hours prior to data collection [[35](#_ENREF_35)].

**2.2.3 *Activity Measures***

Objective PA was measured using Actigraph GT3X accelerometers (Actigraph, Pensacola, FL, USA) located at the level of the wrist and hip for seven consecutive days. A seven-day period was selected to ensure that both measured activity and inactivity were representative of habitual levels [[36](#_ENREF_36)]. A sampling interval (epoch) of three seconds was used as previously outlined in healthy adults [[37](#_ENREF_37)]. The waist accelerometer measured acceleration in three-axial planes and was secured at the participant’s right hip by an elastic belt. The wrist accelerometer was placed on the participant’s dominant arm and was secured using an adjustable velcro strap. The accelerometer units were worn during all waking hours and were only removed when sleeping or during any water activities such as bathing or swimming. Following the seven-day wear period, the accelerometer recordings were downloaded to a computer equipped with Actilife software (Actilife 6 Data Analysis Software, Pensacola, FL, USA).

Accelerometer data were inspected to ensure that information recorded in the logbook corresponded with the accelerometer output. Any activity that was recorded during periods of non-wear time, defined by the participant in the logbook, was deleted [[38](#_ENREF_38)]. Only participants with a minimum of 5 days of monitoring were included in the analyses. These criteria were selected based on the average allowable time previously used to estimate habitual PA in adults [[36](#_ENREF_36)]. Activity outputs were analyzed by determining continuous activity at intensity levels of light, moderate, moderate to vigorous, and vigorous [[37](#_ENREF_37)] PA using cut-off values for each respective intensity level as previously validated in adults. Observations of continuous epochs of “0” counts were considered sedentary time.

**2.2.4 *Anthropometric measurements***

Supine height (cm) was measured to the nearest .5cm without shoes and in light clothing. Body mass was measured to the nearest 0.1kg using a digital wheelchair scale (Detecto Scales, FHD Series, Webb City, Missouri, USA). For participants using either a manual or power wheelchair, weight of both the participant and wheelchair together were recorded, followed by weight of the wheelchair alone and subtracting the wheelchair’s mass to determine the participant’s weight. Body mass index (BMI) was determined by dividing the participant’s weight (kg) by their height (m2) [[39](#_ENREF_39)]. WC, an index of total abdominal fat, was measured to the nearest .5cm in the supine position at the border of the superior iliac crest on the right side of the body following the end of a normal expiration [[40](#_ENREF_40)].

**2.2.5 *Blood Draw***

Following at least 5 minutes of supine rest participants provided blood samples collected into four separate 4 mL red top (clot activator) tubes for serum analysis. Following blood sample collection, the tubes sat idle for 30 min before centrifugation to ensure adequate coagulation. The tubes were then centrifuged at 4000 rpm for 10 min at a temperature of 4oC and 4 mL of serum were aliquotted into 4 separate eppendorf tubes (1 mL per tube) and stored and frozen at -20oC. The samples were analyzed for lipids (cholesterol, HDL, LDL, TC/HDL, triglycerides), the inflammatory marker interleukin (IL)-6, glucose, and insulin, with the latter 2 variables used to calculate HOMA-IR – a marker of insulin resistance [[41](#_ENREF_41)]. Participant lipid labeled eppendorf tubes were sent to Hamilton Regional Laboratory Medicine Program – McMaster Medical Centre Campus for analysis of the previously mentioned markers. The analyte IL-6 was examined using a Quantikine High Sensitivity Human IL-6 ELISA kit (R&D Systems, Inc. Minneapolis, MN, USA). Insulin was examined using the ALPCO immunoassay ELISA kit for the determination of insulin in serum (ALPCO Diagnostics, Salem, NH, USA). Glucose was examined using the Glucose Hexokinase Reagent Set (Pointe Scientific, Inc. Canton, MI, USA). Insulin and glucose concentrations were factored to determine insulin resistance [[41](#_ENREF_41)].

**2.2.6 *Resting heart rate and blood pressure***

Following anthropometric measurements and blood sample collection, participants laid supine for an additional 10 minutes prior to vascular assessments [[35](#_ENREF_35)]. Four measurements of supine brachial artery systolic (SBP), diastolic (DBP), and mean arterial pressures were obtained using an automated sphygmomanometer (Dinamap Pro 100, Critikon LCC, Tampa, Fla, USA). The first measurement was discarded for calibration purposes while the average of the remaining three measures were reported [[42](#_ENREF_42)]. Continuous heart rate via a single-lead electrocardiograph and reconstructed brachial blood pressure measurements via an automated ‘finger cuff’ with oscillometric cuff calibration (Finometer MIDI, Finapres Medical Systems BV, Amsterdam, The Netherlands) were also obtained. All subsequent vascular assessment signals were acquired simultaneously using a commercially available data acquisition system (Powerlab model ML795; ADInstruments, Colorado Springs, CO, USA) and software program (Labchart 7; ADInstruments Inc., Colorado Springs, CO, USA).

**2.2.7 *Vascular measures***

*Carotid distensibility and intima-media thickness*

Carotid distensibility measurements were acquired using a combination of high-resolution, two-dimensional, B-mode ultrasound images with a 10MHz probe (Vivid Q; GE Medical Systems, Horten, Norway) and simultaneous applanation tonometry (model SPT-301; Millar Instruments, Houston, TX, USA). With the participant in a supine position with their mandible elevated, digital images of the left common carotid artery in longitudinal orientation were acquired at a rate of 11 frames/second. A hand-held tonometer was placed over the point of greatest pulsation of the right common carotid artery and held in a fixed position for ten consecutive heart cycles to obtain continuous pressure waveforms. Applanation tonometry is sensitive to the pressure applied by the investigator and generates relative pressure values specific to the site of interest [[43](#_ENREF_43)]. To determine absolute carotid artery systolic blood pressures, the waveforms acquired using applanation tonometry were calibrated to the brachial artery blood pressures acquired simultaneously (Finometer MIDI, Finapres Medical Systems BV, Amsterdam, The Netherlands). When an individual is in a resting supine position, the diastolic and mean arterial pressures are assumed to be consistent in all conduit arteries [[25](#_ENREF_25)]. The brachial artery DBP and mean arterial pressure were equated to the minimum and mean pressures obtained from the right common carotid artery. Using this relationship, the carotid artery SBP was forecasted from the pressure waveforms [[44](#_ENREF_44)].

Ultrasound images were stored offline in Digital Image and Communications in Medicine (DICOM) format for later analysis using a semi-automated edge tracking system [AMS (Artery Measurement System) Image and Data Analysis; Gothenburg Sweden]. This software program was utilized to detect carotid artery lumen diameter within specific regions of interest according to contrasting brightness intensities between the lumen and the walls of the artery [[45](#_ENREF_45)]. After acquiring a region of interest, each frame was scanned to ensure proper placement of the measurement markers and make manual adjustments if necessary. In each frame, carotid artery minimum, mean and maximum lumen diameters were calculated from approximately 100 measurement markers within the region of interest. Distensibility was calculated using the following equation [[46](#_ENREF_46)]:

(1)

where *dmax* represents maximum diameter, *dmin* is the minimum diameter, and PP is the carotid pulse pressure (change in pressure from DBP to SBP). The mean carotid artery diameter was calculated using the average of all diameters acquired from all ten heart cycles. The same software program (AMS) and ultrasound images were used to calculate cIMT. Far-arterial wall IMT was calculated from the proximal aspect of the intima to the proximal interface of the adventitia using the average of the ten frames pertaining to the smallest arterial diameter (end-diastole).

*Pulse wave velocity*

Measurements of resting pulse wave velocity PWV were acquired through simultaneous applanation tonometry and electrocardiography. Both central and peripheral PWV (cPWV, pPWV) were determined from 20 continuous heart cycles using the equation [[46](#_ENREF_46)]:

(2)

Where *D* is the distance between measurement sites and Δ*t* is the pulse transit time (PTT). Arterial pressure waveforms at the common carotid, femoral, radial, and posterior tibialis arteries were collected using simultaneous applanation tonometry on the right side of the body. Tonometry signals were bandpass-filtered (5-30 Hz) with the lower (≤5 Hz) and higher frequencies (≥30 Hz) withdrawn in order to correctly identify the foot of each waveform. The foot of each waveform was identified as the minimum value of the digitally filtered signal and corresponds to the end of diastole - when the steep rise in the wave occurs and appears as a sharp inflection of the original signal [[25](#_ENREF_25)]. Central PTT was determined as the time delay between the arrival of the common carotid pulse wave and the femoral artery pulse wave, with the path distance calculated by subtracting carotid to suprasternal notch distance from suprasternal notch to femoral distance [[47](#_ENREF_47)]. Peripheral PTT was determined as the time delay between the arrival of the femoral artery pulse wave and the posterior tibialis pulse wave [[43](#_ENREF_43)]. Path length was measured as the distance between these two sites, for determining lower-limb pPWV. Upper-limb pPWV was determined by subtracting the carotid-suprasternal notch distance from the suprasternal-radial artery distance. The peripheral PTT was determined as the time delay between the arrival of the carotid artery pulse wave and the radial artery pulse wave. An anthropometric tape was used to measure the distances between superficial skin sites.

*Flow-mediated dilation assessment*

While the participant was in the supine position, the left arm was positioned at an angle approximately 80o from the torso in order to obtain an optimal image of the brachial artery [[48](#_ENREF_48)]. A sphygmomanometric cuff was placed on the left forearm, distal to the medial epicondyle and remained stationary during baseline data collection. Ultrasound images of the left brachial artery approximately 10cm above the antecubital fossa were collected using Duplex ultrasound for simultaneous acquisition of B-mode diameter and pulsed-wave Doppler velocity using a 10MHz linear array probe (Vivid Q; GE Medical Systems, Horten, Norway). All B-mode images were acquired at a rate of 7.7 frames/second. A baseline longitudinal image of the brachial artery was acquired for 30 sec. Prior to recording the baseline image, the brachial artery was imaged using high-resolution B-mode ultrasound to identify clear vascular boundaries. This was performed to permit distinction between the lumen and vessel walls of the artery [[49](#_ENREF_49)]. Modern Duplex ultrasound systems, such as was used in this study, incorporate a narrow Doppler beam aperture that can be steered 20-30o off center of the B-mode imaging beam. This ensures that measurable Doppler shifts are achievable at an angle less than 70o provided extensive flow calibrations have been undertaken [[50](#_ENREF_50)]. The most consistent angle used in this study was of 68o. Upon ideal image detection, the gate width of the steer angle was adjusted accordingly to encompass the entire lumen while minimizing the wall noise of the vessel.

To create a flow stimulus, the forearm cuff was instantaneously inflated to a suprasystolic pressure of 200mmHg to ensure arterial occlusion and ischemia of downstream tissue [[51](#_ENREF_51)]. A cuff occlusion time of 5 minutes performed distally to the ultrasound probe has been associated with a significant FMD response and variations to the duration, magnitude, and placement of the cuff will result in varying FMD responses due to dilators other than NO [[52](#_ENREF_52)]. At the 4 minute time point of occlusion, a 30 sec image was recorded using Duplex ultrasound. At 5 minutes, the cuff was instantaneously deflated and Duplex images were recorded for 3 minutes to capture both hyperemic blood velocity and peak arterial diameter. The velocity signals were processed by an external spectral analysis system (Neurovision 500M, Multigon Ind; Yonkers NY) and an intensity-weighted calculated mean was outsourced to the Powerlab data acquisition system.

The baseline, 4 minute, and post-occlusion images were stored offline as DICOM files. End-diastolic frames were extracted from each of the three images using a DICOM editing software program (Sante DICOM Editor 3.1.13, Santescroft, Athens, Greece). AMS was used to detect near and far wall adventitia within a specific region of interest for the end-diastolic frames as each time point. The peak dilation of the vessel at baseline and at 4 min was taken as an average of the frames recorded in their respective 30 sec image. To obtain the peak diameter after cuff release, 5-s time bins were calculated with the peak designated as the largest 5-s bin [[53](#_ENREF_53)]. The absolute FMD (mm) and relative FMD (%FMD) were calculated as follows:

*Absolute FMD = Peak Diameter (mm) – Baseline Diameter (mm)*

*Relative FMD* = (3)

The magnitude of the shear rate stimulus is proportional to the relative FMD response [[48](#_ENREF_48)]. The following equation was used to calculate shear rate for each subject:

Shear Rate = 8 x (4)

Where velocity and diameter represent the mean velocity and internal arterial diameter for a specific frame. The area under the curve of the shear rate was calculated using the trapezoid rule to obtain the area under the curve up until peak diameter during cuff release (GraphPad PRISM version 5.0a. La Jolla, CA, USA).

Relative FMD (%FMD) was normalized to the area under the entire shear rate curve to account for baseline diameter.

*NormalizedFMD=*  (5)

**2.2.8 *Statistical analysis***

Statistical analysis was performed using SPSS software (SPSS 20. IBM, Armonk, NY, USA). All continuous variables were tested for normality using Shapiro-Wilks descriptive test. Data was originally separated into five groups based on the GMFCS. The GMFCS levels assess activity limitations pertaining to gross motor function with a five-level ordinal scale [1]. Individuals with GMFCS level I can typically walk without significant restrictions. Conversely, those with GMFCS level V are very restricted in their ability to function physically. The GMFCS has been validated as a reliable tool for use in the adult population with a strong inter-rater reliability [[54](#_ENREF_54), [55](#_ENREF_55)]. Differences in anthropometrics, vascular indices, activity levels, and metabolic markers were analyzed using one-way ANOVA with Tukey post hoc procedures.

When performing one-way ANOVA, samples are more susceptible to unequal variances when the size of the population within each group is small or when sample sizes are unequal [[56](#_ENREF_56)]. Increasing the sample size within each group has been shown to mitigate the chance of committing a type I error. Data was collapsed into two groups based on whether participants were community ambulant or non-ambulant based on previous studies that have suggested those in GMFCS levels III-V prefer to use wheeled devices to move about in the community [[57](#_ENREF_57), [58](#_ENREF_58)]. Upon separation into two groups, data was reassessed for normality and independent t-tests were performed on the same variables.

To determine the independent contribution of historical CVD risk attributes (age, WC, MVPA/hour) as well as the novelty of the CP population (GMFCS level) on these cardiovascular and cardiometabolic outcomes, separate multiple regression analyses were conducted for each dependent variable (i.e. each vascular and metabolic marker) using a backward regression model. Numeric coding was applied to the categorical variable GMFCS (GMFCS levels I-II=0 or GMFCS levels III-V=1). For each model, standardized regression coefficients were determined. Further, percent variance attributable to the main outcome within each model was tested using an analysis of variance to determine the significance of each model. If there was greater than one independent predictor for a particular model, a forward regression analysis was performed to determine which predictor represented the greatest variance. Data are reported as means ± SD. A minimum criterion alpha level of *P*≤0.05 was used to determine statistical significance.

**2.3 RESULTS**

**2.3.1 *Participant Characteristics***

The sample population, separated into two groups based on whether participants were community ambulant (GMFCS I-II) or non-ambulant (GMFCS III-V), were of similar age, body mass, WC, and BMI (Table 1). The ambulant group was taller than the non-ambulant group (p=0.013) (Table 1). There were no group differences between SBP, DBP or mean arterial pressure. The non-ambulant group had a higher resting, supine heart rate (p=0.05) (Table 1).

**2.3.2 *Physical Activity***

The total amount of minutes of wear time/day, moderate-to-vigorous physical activity (MVPA)/day, sedentary time/day, MVPA/hour, and sedentary time/hour are reported in Table 2. The ambulant participants wore the device for a greater duration per day compared to the non-ambulant group (p=0.033) (Fig. 1A). Furthermore, the ambulant group engaged in more MVPA/day (p=0.001) (Fig. 1B) and MVPA/hour (p=0.001) than the non-ambulant group (Fig. 1C). Sedentary time/day was not different between groups, however, after controlling for wear time, the non-ambulant group engaged in more sedentary time/hour than the ambulant group (p=0.001) (Fig. 1D).

**2.3.3 *Vascular Indices***

There were no differences in carotid artery distensibility or IMT between groups (Table 3). One non-ambulant CP participant was removed from these vascular assessments due to severe spasticity of the upper extremities resulting in inadequate ultrasound image quality. There were no group differences in central PWV (Table 3). Two ambulant and five non-ambulant participants were removed from the central and lower limb PWV analysis as a result of inadequate tonometry signals. No differences were observed in lower-limb PWV (Table 3), however upper-limb PWV was higher in the non-ambulant group indicative of an increase in arterial stiffness compared to the ambulant group (p=0.006) (Fig. 2). Two ambulant and three non-ambulant participants were removed from the upper-limb PWV analysis due to inadequate tonometry signals (Table 3).

There were no between-group differences in pre-occlusion brachial artery diameter (mm) or peak brachial artery diameter (mm) achieved during reactive hyperemia (Table 3). Furthermore, there were no differences between groups in absolute FMD (mm), relative FMD (%), normalized FMD (%FMD/SRAUC), or SR stimulus (Table 3).

**2.3.4 *Cardiometabolic Blood Markers***

There were no between group differences for all metabolic markers assessed. Glucose (CV 8.8%), insulin (CV 8.2%), HOMA-IR, IL-6 (CV 9.0%) and lipid marker concentrations are reported in Table 4. Blood draws were not acquired on 1 ambulant and 7 non-ambulant participants for glucose, insulin, HOMA-IR and IL-6 due to contractures, spasticity, or vein size. An additional non-ambulant participant was not included in the lipid analysis (n=31) as a result of insufficient serum content to perform the assessment. Both group means were below the target HDL-C level of 1.30 mmol/L.

**2.3.5** ***Multiple linear regression coefficients***

Further analysis was performed to determine if traditional risk factors (age and WC), as well as gross motor function classification and PA (MVPA/hour), were predictive of cardiovascular outcomes (Table 5). When controlling for age, WC, and time spent in MVPA/hour, GMFCS was an independent predictor of HR (β=.31; p=0.05) (Fig. 3A) and upper-limb PWV (β=.46; p=0.006) (Fig. 3B). When controlling for WC, MVPA/hour, and GMFCS, age was an independent predictor of SBP (β=.36; p=0.02) (Fig. 4A), mean arterial pressure (β=.42; p=0.007) (Fig. 4B), central PWV (β=.70; p=0.001) (Fig. 4C), IMT (β =.76; p=0.001) (Fig. 4D), and distensibility (β=-.38; p=0.02) (Fig. 4E). When controlling for age, GMFCS, and MVPA/hour, WC was an independent predictor of HDL-C (β=-.50; p=0.006) (Fig. 5A), LDL-C (β=.54; p=0.001) (Fig. 5B), triglycerides (β=.54; p=0.002) (Fig. 5C), TC/HDL-C ratio (β=.72; p=0.001) (Fig. 5D), IL-6 (β=.41; p=0.02) (Fig. 5E), and HOMA-IR (β=.40; p=0.025) (Fig. 5F). Finally, when controlling for age, GMFCS, and WC, MVPA/hour was an independent predictor of DBP, mean arterial pressure, triglyceride level, and HOMA-IR. However, when placed in a forward regression to determine which independent variable was the strongest predictor, MVPA/hour was not found to be a significant predictor of any outcome variable (Table 6).

Table 1

Subject Characteristics

|  |  |  |  |
| --- | --- | --- | --- |
|  | GMFCS I-II (n=14) | GMFCS III-V (n=26) | P Value |
| Gender | 8/6 (M/F) | 13/13 (M/F) | 0.376 |
| Age, yrs | 31.7 ± 10.4 | 34.8 ± 13.6 | 0.464 |
| Height, m | 1.67 ± .10 | 1.57 ± .12\* | 0.013 |
| Mass, kg | 69.7 ± 21.1 | 63.9 ± 24.3 | 0.461 |
| Resting HR, bpm | 71.9 ± 9.3 | 79.8 ± 13.4\* | 0.050 |
| Resting Systolic BP, mmHg | 123.2 ± 9.9 | 124.3 ± 19.0 | 0.848 |
| Resting Diastolic BP, mmHg | 73.1 ± 8.8 | 74.5 ± 9.0 | 0.648 |
| Resting MAP, mmHg ⌘ | 91.9 ± 6.8 | 93.6 ± 11.4 | 0.676 |
| BMI, kg/m2 ⌘ | 24.7 ± 5.9 | 25.5 ± 8.4 | 0.900 |
| WC, cm | 83.9 ± 17.4 | 85.9 ± 18.6 | 0.835 |

Values are represented as means ± SD. HR, heart rate; BPM, beats per minute; BP, blood pressure; MAP, mean arterial pressure; BMI, body mass index; WC, waist circumference.

⌘ Logarithm transformation performed

\*p≤0.05

Table 2

Group comparisons of daily and hourly physical activity levels

|  |  |  |  |
| --- | --- | --- | --- |
|  | GMFCS I-II (n=14) | GMFCS III-V (n=26) | P value |
| Wear time/day, minψ | 736.2 ± 124.9 | 648.8 ± 119.6\* | .033 |
| MVPA/day, min⌘ | 29.6 ± 28.4 | 3.23 ± 6.54\* | .001 |
| Sedentary time/day, min⌘ | 630.8 ± 111.6 | 625.8 ± 122.6 | .861 |
| MVPA/hour, min⌘ | 2.36 ± 2.13 | 0.32 ± 0.64\* | .001 |
| Sedentary time/hour, min♯ | 51.6 ± 4.71 | 57.8 ± 1.94\* | .001 |

Values are represented as means ± SD. MVPA, moderate to vigorous physical activity.

Ψ Square transformation performed

⌘ Logarithm transformation performed

♯Mann-Whitney U test was performed on non-normally distributed data

\*p<0.05

Table 3

Group comparisons of FMD response, carotid distensibility and IMT, central, lower and upper PWV

|  |  |  |  |
| --- | --- | --- | --- |
|  | GMFCS I-II | GMFCS III-V | P Value |
| Pre-occlusion diameter, mm | 3.60 ± .56 | 3.40 ± .58 | 0.310 |
| 4min diameter, mm | 3.56 ± .56 | 3.37 ± .59 | 0.344 |
| RH peak diameter, mm | 3.90 ± .56 | 3.68 ± .53 | 0.248 |
| Absolute FMD, mm | 0.30 ± .13 | 0.28 ± .15 | 0.741 |
| Relative FMD (%FMD)♯ | 8.6 ± 4.3 | 8.9 ± 5.5 | 0.838 |
| Normalized (%FMD/SRAUC)♯ | 7.2e-4 ± 1.6e-3 | 2.5e-3 ± 7.8e-3 | 0.397 |
| Mean SR♯ | 34500 ± 19230 | 31022 ± 29529 | 0.181 |
| Distensibility, mmHg-1⌘ | 4.7e-3 ± 4.3e-3 | 3.4e-3 ± 1.4e-3 | 0.216 |
| IMT, mm | .49 ± .10 | .55 ± .17 | 0.189 |
| Central PWV (m/s) | 6.23 ± .50 | 6.69 ± 1.47 | 0.305 |
| Lower PWV (m/s) | 8.30 ± 1.49 | 8.37 ± 1.85 | 0.923 |
| Upper PWV (m/s) | 8.28 ± 1.61 | 10.2 ± 1.92\* | 0.006 |

Values are represented as means ± SD. RH, reactive hyperemia; FMD, flow mediated dilation; SR, shear rate; SRAUC, shear rate area under the curve; IMT, intima media thickness; distensibility (GMFCS I-II n=14)(GMFCS III-V n=25). PWV, pulse wave velocity, central and lower (GMFCS I-II n=12)(GMFCS III-V n=21). Upper (GMFCS I-II n=12)(GMFCS III-V n=23).

♯Mann-Whitney U test was performed on non-normally distributed data

⌘ Logarithm transformation performed

\*p<0.05

Table 4

Group comparisons of glucose, insulin, HOMA-IR, IL-6, and lipid concentrations

|  |  |  |  |
| --- | --- | --- | --- |
|  | GMFCS I-II | GMFCS III-V | P Value |
| Glucose, mg/dL | 99.14 ± 9.49 | 101.10 ± 17.79 | 0.719 |
| Insulin, μIU/mL ♯ | 7.39 ± 4.62 | 10.7 ± 16.0 | 0.910 |
| HOMA-IR, mass units ⌘ | 1.77 ± 1.04 | 2.82 ± 4.40 | 0.652 |
| IL-6, pg/mL ⌘ | 2.76 ± 2.87 | 2.04 ± 1.51 | 0.545 |
| Cholesterol, mmol/L | 4.98 ± .98 | 4.84 ± 1.08 | 0.714 |
| Triglycerides, mmol/L ⌘ | 1.11 ± .55 | 1.23 ± .68 | 0.659 |
| HDL-C, mmol/L | 1.26 ± .23 | 1.15 ± .25 | 0.204 |
| LDL-C, mmol/L | 3.21 ± .84 | 3.13 ± .88 | 0.795 |
| TC/HDL-C ratio | 4.09 ± 1.2 | 4.36 ± 1.3 | 0.523 |

Values are represented as means ± SD. HOMA-IR, Homeostasis model assessment insulin resistance; IL-6, Interleukin 6 (GMFCS I-II n=13)(GMFCS III-V n=19). HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC/HDL-C, total cholesterol to high density lipoprotein cholesterol (GMFCSI-II n=13)(GMFCS III-V n=18).

⌘ Logarithm transformation performed  
♯ Mann-Whitney U test was performed on non-normally distributed data

Table 5

Backward multiple linear regression



  



Table 6

Forward multiple linear regression





**Figure 1** A.)Group comparison of accelerometer wear time per day

B.) Group comparison of minutes of MVPA per day

C.) Group comparison of minutes of MVPA per hour

D.) Group comparison of sedentary time per hour

ambulant n=14, non-ambulant n=26

\*p<0.05



**Figure 2.** Group comparison of upper PWV; ambulant n=12, non-ambulant n=23

\*p<0.05



**Figure 3** A.) GMFCS as an independent predictor of heart rate; n=40

B.)GMFCS as an independent predictor of upper-limb PWV; n=35



**Figure 4** A.) Age as an independent predictor of SBP; n=40

B.) Age as an independent predictor of MAP; n=40

C.) Age as an independent predictor of central PWV; n=32

D.) Age as an independent predictor of IMT; n=39

E.) Age as an independent predictor of distensibility; n=39



**Figure 5** A.) Waist circumference as an independent predictor of HDL-C; n=31

B.) Waist circumference as an independent predictor of LDL-C; n=31

C.) Waist circumference as an independent predictor of triglycerides; n=31

D.) Waist circumference as an independent predictor of TC/HDL-C; n=31

E.) Waist circumference as an independent predictor of IL-6; n=32

F.) Waist circumference as an independent predictor of HOMA-IR; n=32

**2.4 DISCUSSION**

Prolonged exposure to decreased PA levels in the general population is associated with impairments of vascular health and increased cardiovascular risk, and many individuals with CP may be in a lifelong state of physical limitation resulting in chronically decreased PA. The primary novel findings of this study were that clinically significant measures of vascular health and blood markers of cardiometabolic risk were not different between community ambulant (GMFCS I-II) and non-ambulant (GMFCS III-V) adults with CP. These lack of group differences in cardiovascular disease risk factors were observed in the face of the non-ambulant group spending significantly less time performing MVPA and having increased sedentary time per hour compared to the ambulant group.

The present cross-sectional observational study is the first to characterize indices of vascular health in adults with CP (33.7 ± 12.5 yrs, min-max 18-75) across the complete range of the GMFCS scale (I-V). Previous research has shown that adults with CP have a near threefold increased death rate from coronary disease compared to the general population [[31](#_ENREF_31)]. A lack of prospective and longitudinal studies makes it difficult to infer the causation of coronary disease related deaths in adults with CP. We hypothesized that chronic reductions in PA in this population, as a result of their physical impairment, may be an underlying cause. Recent research has documented decreased PA levels in adults with CP compared to healthy active peers, even in the highest functioning CP population [[6](#_ENREF_6)]. In the general population, decreased PA levels have been correlated with increased arterial stiffness, endothelial dysfunction, and carotid artery wall thickness [[14](#_ENREF_14), [59](#_ENREF_59), [60](#_ENREF_60)]. Current PA guidelines suggest 150 min of MVPA per week as the minimum to promote health benefits [[61](#_ENREF_61)]. According to these guidelines, our sample of ambulatory adults with CP is achieving the minimum levels required for health benefits (mean 210 min/week) while the non-ambulatory participants are far below that level (23 min/week) and would be predicted to be at an elevated risk of CVD.

MVPA levels and sedentary time per hour were different between the two groups, with the ambulatory group having increased MVPA and reduced sedentary time per hour. Lack of PA is the second leading behavioural cause of death in America [[62](#_ENREF_62)]. It is apparent that PA levels decline from childhood into the adult years in the general population [[8](#_ENREF_8)], and this may be exacerbated in the CP population. Participants in the non-ambulatory group spent 96% of their time within an hour in the sedentary state. Sitting time has been shown to be positively associated with resting heart rate in a cohort with similar age to the present study. Average MVPA values in our ambulant group were 29.6 ± 28.4 min/day that would adhere to the required 150 minimum of MVPA suggested for health benefits in adults [[61](#_ENREF_61)]. These values would appear to be larger than those reported from a Dutch cohort of ambulant CP subjects, in which they reported activity levels that were 85% of the able-bodied aged reference sample [[7](#_ENREF_7)]. It should be noted, however, that time spent in the sedentary state may not represent inactivity for the CP population. Adults with CP may use increased intentional muscular activity to maintain a seated posture and the increased atypical muscle tone (i.e. spasticity) present in adults with CP likely elevates energy expenditure during sitting [[63](#_ENREF_63)]. Therefore, we cannot assume that persons with CP are ‘sedentary’ while sitting. There are three inherent factors within the definition of sedentary behaviour: (1) Posture (sitting or reclining); (2) Energy expenditure (≤ 1.5 metabolic equivalents); and (3) Muscular inactivity [[63](#_ENREF_63)]. Perhaps the muscular demands required for some individuals with CP to maintain their balance while sitting are large enough to label sitting as non-sedentary. This would suggest that the muscle activity elicited while sitting may provide enough cardiovascular benefit to note the lack of differences in endothelial function and central stiffness between the ambulant and non-ambulant groups in the present study. Future interventional studies in the CP population suggest replacing time spent in the sedentary state, or sitting, with standing exercises that require large muscle groups to remain under tension.

With respect to body composition, men are at an increased risk for CVD if they present a WC greater than 102cm; women are at an increased risk if they have a WC greater than 88cm [[40](#_ENREF_40)]. In the current study there was no difference in WC between the two groups. While the mean of each group was below the risk cut-off of 88cm, the standard deviations were quite large (Table 1). Individual data shows that 5 males (2 ambulant, 3 non-ambulant) and 7 females (2 ambulant, 5 non-ambulant) were at elevated risk of CVD based on their WC values. BMI has been scrutinized as a means of determining normal, obese, or overweight values in certain populations [[64](#_ENREF_64)]. For older individuals, WC assumes greater value for estimating risk of obesity-related diseases [[40](#_ENREF_40)]. Furthermore, Peterson *et al*. rationalized that waist-to-hip ratio was a better overall predictor of cardiometabolic risk than both BMI and WC in adults with CP [[32](#_ENREF_32)]. Contrary to this, van der Slot *et al*. recently showed that WC was the strongest independent predictor of systematic coronary risk evaluation in adults with CP [[33](#_ENREF_33)]. Regardless, according to BMI cut-offs 7 individuals were overweight (BMI 25.0–29.9), 4 were obese level I (BMI 30.0–34.9), 4 were obese level II (BMI 35.0–39.9), and 1 was extremely obese (BMI >40.0). In contrast, 9 participants were underweight (BMI <18.5) with 6 of those in the non-ambulant group. Peterson *et al*., also found that BMI was lowest in the adults with lower gross motor function (GMFCS IV-V) [[32](#_ENREF_32)]. In our cohort, while both groups appeared healthy with respect to average resting systolic and diastolic blood pressures 6 participants had an SBP ≥140mmHg and 3 of those also had a DBP ≥90mmHg.

In the current study, no significant differences were found between groups for central or lower-limb PWV and our values were comparable to reference values for the general population determined from 245 normotensive participants aged 30-39 years (PWV = 6.5 ± 1.4 m/s) [[65](#_ENREF_65)]. Although MVPA levels and sedentary time/hour were different between our groups, age was the only significant independent predictor of central PWV using multiple linear regression analysis. Perhaps the relatively young adult age of the participants explains the comparable stiffness values to reference values. Previous research has shown a negative relationship between PA levels and arterial stiffness in the adult population [[66](#_ENREF_66)]. As resting energy expenditure and physical strain are elevated in CP, perhaps the greater effort required to perform tasks attenuates arterial stiffening [[67](#_ENREF_67)].

We did, however find that upper-limb arterial stiffness was increased in the non-ambulant group. Research has shown that exercise training interventions in older adults results in decreases in central arterial stiffness only with no changes observed in upper- or lower-limb PWV [[14](#_ENREF_14)]. It is difficult to speculate why the ambulant group, with higher MVPA levels, would have similar central PWV values but reduced upper PWV compared to the non-ambulant group. It has been shown in a sample of young females (18-30yrs) that increased muscle sympathetic nervous system activity was correlated with elevated inflammatory markers and peripheral arterial stiffness [19]. This could possibly explain the increase in upper-limb stiffness, particularly in the lower functioning non-ambulant group where increased sympathetic nervous system activity has been identified [68], however this theory is not supported by group differences in blood pressure indices. We also found that severity of gross motor function (GMFCS level) was the strongest independent predictor of upper limb stiffness in this cohort and this relationship was present after adjusting for age, MVPA per hour, and WC.

Carotid distensibility is an estimate of local arterial elasticity and has been shown to increase in children, adolescents, and young adults, plateaus near age 30, and begins to decline thereafter [[69](#_ENREF_69)]. Perhaps the fact that both groups were relatively young, age associated decreases in distensibility may not be apparent. It is important to note, however, that age was the only significant independent predictor of distensibility, explaining 14.3% of the variance.

There is an apparent progressive deterioration in endothelial function with aging that can be resultant of endothelial cell hyperplasia and atherosclerosis [[25](#_ENREF_25)]. In the present study, there was no difference between the two groups with respect to endothelial function. Improved endothelial function that is seen with exercise training is attributed to increased expression of the enzyme NOS in response to increased endothelial shear stress associated with exercise [[71](#_ENREF_71)]. It may be that endothelial function was maintained in the higher functioning GMFCS I-II who attained roughly 30 min of MVPA per day. In contrast it is difficult to explain why the lower functioning group maintained similar levels of endothelial function. Acetylcholine has been referenced as a stimulus for the release of NO from the endothelium, which would subsequently promote smooth muscle relaxation and vasodilation [[23](#_ENREF_23)]. Research has shown that acetylcholine receptors are elevated in children with CP, in areas distal to the neuromuscular junction [[72](#_ENREF_72)]. Muscanaric acetylcholine receptor levels have not been identified in the CP population, but this could possibly explain a preservation of endothelial function in the lower functioning group.

Age has been previously identified as the strongest predictor of carotid IMT [[73](#_ENREF_73)] and in the current study age explained 57.5% of the variance associated with IMT, which was independent of PA, WC, and GMFCS levels. Tanaka and colleagues showed that there was no difference in carotid IMT between healthy sedentary and endurance trained individuals within the same age group (54 ± 2 yrs) and that IMT remained the same after the sedentary group underwent a 3 month exercise training intervention [[18](#_ENREF_18)]. In agreement we did not observe group differences in IMT despite the higher functioning group being more physically active. It has also been identified that having a carotid IMT greater than 0.82mm increased the risk of myocardial infarction, stroke, and peripheral artery disease in a cohort of middle-aged Finnish men [[74](#_ENREF_74)]. Three subjects in the current study, all in the non-ambulant group, presented an IMT greater than 0.82mm.

There were no group differences in lipid profiles between the two groups, nor were there differences in glucose, insulin, or IL-6 concentrations. Average cholesterol levels in both groups were below clinical minimum levels (<5.20 mmol/L), however, average HDL-C levels were below the target level of 1.30 mmol/L. Both groups were classified at low risk for CVD by having average LDL-C levels below 3.40 mmol/L and both groups were below the low risk level of 6.0 for TC/HDL-C ratio. In agreement with previous literature [12], when adjusted for age, GMFCS, and MVPA levels, participants with a higher WC were predictive of having higher LDL-C, triglyceride levels, TC/HDL-C ratio, IL-6 and lower HDL-C. There was no evidence for associations between MVPA levels and vascular or metabolic health. This absence of predictability may be a result of the relatively young age of the study sample and our small sample size. The inclusion of lower functioning persons produced broader ranges of MVPA levels, however, PA was overpowered by traditional predictors of vascular and metabolic markers such as age and WC in terms of predictive capacity in the regression analysis.

Previous literature has documented that adults with CP are significantly shorter than healthy controls, likely due to reduced growth maturation seen in children with CP in that it persists to adulthood [[75](#_ENREF_75), [76](#_ENREF_76)]. Although previous studies examining stature did not separate participants using the GMFCS, those with the greatest impairments, evident through a specialized feeding apparatus, were shortest in height [76]. Our current results also suggest that adults with CP who are lower functioning tend to be shorter than their higher functioning peers. This shorter stature is likely resultant of the inability of contracted muscles to remain in parallel with bone growth, leading to joint deformities and reduced ambulation.

We have demonstrated that although age was the strongest independent predictor for the majority of the vascular outcome variables, GMFCS showed a trend towards significance and may be a predictor in a larger and older cohort of adults with CP. Of particular interest would be further research in the non-ambulant group, who presented with elevated resting heart rate and upper limb arterial stiffness. A faster heart rate over time has been associated with an increased progression of collagen formation in the central arteries as a result of constant pressure loads [[25](#_ENREF_25)]. However, our postulation that increased acetylcholine receptors in those with CP may attenuate the progression of endothelial dysfunction as mediated through increased enzyme NOS activity and subsequent vasodilation and the predictive use of assessments of vascular health in adults with CP warrant further investigation.

**2.4.1 *Limitations***

Although the vascular health assessment methodology performed in the current study is relatively straightforward, limitations to the procedure vary and encompass both technical and interpretive challenges. Data are largely dependent on the quality of the ultrasound images and require a skilled operator and appropriate equipment and analysis software. The current results are limited to adults with CP across the entirety of the GMFCS scale. Specific technical difficulties that were incurred included contractures and spasms in the musculature of the imaged arm that may have hindered image quality and impacted on outcomes. Regarding measurement of PA, it is difficult to state whether the accelerometer captured true habitual PA, specifically in those whom were lower functioning. The accelerometers may not have been worn during transfer activities and were certainly not worn during water activities – two instances when activity may be greatest for persons who are lower functioning (i.e GMFCS V).

**2.4.2 *Future Directions***

Despite significant differences in MVPA levels and sedentary time/hour, there were no differences in central or lower-limb stiffness, brachial artery endothelial function, and cardiometabolic markers between groups, indicating a disconnect between levels of PA and vascular indices of health in this cohort of adults with CP. This disconnect may be due to the fact that the adult cohort studied was relatively young, and the effects of inactivity in the non-ambulant group may not compromise vascular health this early in life. Furthermore, we did not assess light PA in this study, which could possibly explain the preservation of endothelial function in the non-ambulant group. However, the fact that 96% of the time was spent in the sedentary state suggests that the non-ambulant group was performing very little, if any, activity while wearing the accelerometers. The long term preservation of sedentary behavior in the non-ambulant group may have deleterious consequences on vascular health in the later adult years and warrants further longitudinal investigation.

**2.4.3 *Conclusion***

In agreement with the literature in the general population age was the strongest independent predictor for the majority of the vascular outcome variables in our cohort of adults with CP. However, the novel finding in this study was that GMFCS was an independent predictor of both uPWV and resting heart rate in this cohort of subjects. GMFCS may be a stronger independent predictor in larger, older cohorts of adults with CP, specifically in lower functioning individuals who experience minimal MVPA and increased sedentary time. It is important to highlight the establishment of techniques to assess arterial health in adults with CP, which is critically important for determining future cardiovascular risk in this clinical population. This study confirms the feasibility of using these vascular assessment techniques in this population and identifies the potential for future, longitudinal assessments of adults with CP across the entire GMFCS scale.

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**APPENDIX A – GMFCS Self Report Questionnaire for Adults Aged 18 years and**

**Older**

Please read the following and mark **only one box** beside the description that best represents your own movement abilities.

I,

􀂉 **Have difficulty sitting on my or his/her own and controlling my head and body posture in most positions**

**and** have difficulty achieving any voluntary control of movement

**and** need a specially adapted chair to sit comfortably and be transported anywhere

**and** have to be lifted or hoisted by another person or special equipment to move

􀂉 **Can sit with some pelvic and trunk support but do not stand or walk without significant support**

**and** therefore always rely/relies on wheelchair when outdoors

**and** can achieve self-mobility using a powered wheelchair

**and** can crawl or roll to a limited extent to move around indoors

􀂉 **Can stand on my own and walk if using a hand-held walking aid** (such as a walker, rollator, crutches, canes, etc.)

**and** find it difficult to climb stairs, or walk on uneven surfaces without support

**and** use a variety of means to move around depending on the circumstances

**and** prefer to use a wheelchair to travel quickly or over longer distances

􀂉 **Can walk on my own without any walking aids, but need/needs to hold the handrail when going up or down stairs**

**and** therefore walks in most settings

**and** often finds it difficult to walk on uneven surfaces, slopes or in crowds

**and** may occasionally prefer to use a walking aid (such as a cane or crutch) or a wheelchair to travel quickly or over longer distances

􀂉 **Can walk on my own without using walking aids, and can go up or down stairs without needing to hold the handrail**

**and** walk wherever they want to go (including uneven surfaces, slopes or in crowds)

**and** can run and jump although their speed, balance, and coordination may be limited

**APPENDIX B – Letter of Information / Consent**

**A study of physical activity, cardiovascular health and obesity in adults with cerebral palsy aged 20-40**

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**Why is this research being done?**

This research is being conducted as part of a larger study called the Stay-FIT research program, led by Dr. Jan Willem Gorter at the *CanChild Centre for Childhood Disability Research* at McMaster University. The goal of the Stay-FIT study is to understand and ultimately reduce the risk of cardiovascular disease in individuals with cerebral palsy (CP) and to develop community-based programs for youth with CP that promote physical activity and healthy living across the lifespan.

Leading a physically inactive lifestyle can increase a person’s chance of developing cardiovascular disease and obesity. We know that the mobility limitations associated with CP have an impact on physical activity. Adolescents with CP are less physically active than their healthy peers. This may put adolescents at risk of developing cardiovascular disease and it has already been shown that obesity among children with CP has risen over the last decade. There is very little research, however, on the cardiovascular health of adults with CP. We therefore want to learn more about how the physical activity levels of adults with CP impact their health. We are particularly interested in measuring risk factors for cardiovascular disease and obesity.

**What is the purpose of this study?**

The results obtained in this study will provide some insight into the relationship between physical activity, cardiovascular health, and obesity in adults with CP aged 20-40 years who have varying degrees of mobility spanning all levels of the GMFCS spectrum (I-V).

**What will happen during this study?**

If you decide to volunteer to participate in this study, we will ask you to do the following things:

* Schedule **1 visit** to the Department of Kinesiology at McMaster University.
* Before your scheduled visit we will give you a small pager-like device called an **accelerometer** to wear on your wrist and around your waist for 7 days prior to your visit. This device will automatically send us information on your physical activity levels throughout the week. We will also give you a **logbook** so that you can keep track of when you take off the accelerometer, for example, when you go to sleep at night. The accelerometer is to be returned at your visit.
* We will require you to have fasted for 12 hours prior to your arrival. Specific requirements can be found on the accompanying page “Participant Guidelines for Fasting.”
* At the visit, we will ask you to step on a scale to measure your **weight**. We will also measure your **height** and the size of your **waist.**
* Next, we will provide you with a short **questionnaire** that will ask you about the levels of fatigue you experience in a typical week.
* Following the questionnaire we will conduct an **interview** about the type, frequency, duration, and intensity of physical activity you do throughout the week. This interview will take about 20 to 25 minutes to complete.
* Then we will ask to take a **blood sample** from a vessel in your arm (located at the inside of the elbow) to measure the amount of lipids, insulin, Vitamin D, and glucose in your bloodstream.
* We will then measure the **health of the main blood vessels in your neck and arm** using a non-invasive **ultrasound machine**. These vascular health tests will require that you lie on a bed for about 20 minutes while the measurements are taken.

**What are the possible risks and discomforts?**

The risks involved in participating in this study are minimal. The ultrasound machine used to measure the health of your blood vessels is the same machine used on mothers to take pictures of their babies when they are pregnant. You will not feel any pain, however we will need to put some special jelly on your skin in order to take the pictures, which may feel cold at first.

You may experience a small, pinching-type pain when the needle is inserted into your arm to draw your blood, but this should last no longer than a few seconds.

You may experience discomfort during one of the vascular measurements, called a flow-mediated dilation (FMD) assessment. This test will require that we occlude the blood flow to your hand for five minutes using a blood pressure cuff on your forearm. You may feel a tingling sensation or no feeling at all during these five minutes, a sensation similar to when your hand or foot fall asleep. No permanent damage or pain will result from this and any discomfort will go away as soon as the five minutes is over.

It is not likely that there will be any harms or discomforts associated with wearing the accelerometer around your waist and wrist. However, you may find it inconvenient at first.

Remember that you will not be forced to do anything that makes you feel uncomfortable and you have the right to stop taking part in the study at any time. I describe below the steps I am taking to protect your privacy.

**Are there any benefits to doing this study?**

Although we cannot promise any personal benefits to you from your participation in this study, you will get the opportunity to learn more about the health of your blood vessels and your body composition. These measurements are important for your health and can be improved with physical activity. You will also be able to see for yourself how much physical activity you do in a typical week.

By participating in this study, you will help us to understand the relationship between barriers to physical activity in cerebral palsy and risk for cardiovascular disease and obesity. We hope to use this information in order to create community-based programs for youth with CP that will promote the importance of physical activity and a healthy lifestyle and ultimately, prevent the risk of developing these diseases amongst individuals with CP later in life.

**Payment or Reimbursement**

We will reimburse you for any travel costs and parking expenses you may incur in getting to McMaster University. We will reimburse these expenses even if you decide that you no longer want to participate part-way through the study.

**Who will know what I said or did in the study?**

You are participating in this study confidentially. Your name will not be used, nor will there be any information published that would allow you to be identified. No one but Dr. Jan Willem Gorter, and the research assistants involved in the project will know whether you participated unless you choose to tell them.

The information you provide will be kept in a locked desk/cabinet where only the investigators and research assistants will have access to it. Information kept on a computer will be protected by a password. Once the study has been completed, the data will be securely stored and will be destroyed after 10 years. If the results of the study are published, your identity will remain confidential.

**What if I change my mind about being in the study?**

It is your choice to be a part of this study or not. If you decide to participate, you have the right to stop (withdraw) at any time and for whatever reason, even after signing the consent form or part-way through the study. If you decide to withdraw, there will be no consequences to you whatsoever and no one will judge you.

In cases of withdrawal, any data you have provided will be destroyed unless you indicate otherwise. If you do not feel comfortable doing something, you do not have to do it and will not be forced to, however please note that you can still be in the study if this is the case.

**How do I find out what was learned in this study?**

If you would like a brief summary of your results, please provide your preferred contact information at the end of this form and the results will be sent to you upon completion of the project.

**If I have any questions or concerns, whom can I call?**

If you have questions or need more information about the study itself, please do not hesitate to contact Dr. Jan Willem Gorter at **(905) 521-2100 x 27855**or [gorter@mcmaster.ca](mailto:gorter@mcmaster.ca)

This study has been reviewed by the Hamilton Integrated Research Ethics Board (HIREB) and received ethics clearance.

If you have concerns or questions about your rights as a participant or about the way the study is conducted, please contact:

Office of the Chair of the HIREB

Telephone: (905) 521-2100 ext. 42013

**CONSENT**

I have read the information presented in the information letter about a study being conducted by Dr. Jan Willem Gorter at McMaster University.

I have had the opportunity to ask questions about my involvement in this study and to receive additional details I requested.

I understand that if I agree to participate in this study, I may withdraw from the study at any time. I will be given a signed copy of this form. I agree to participate in the study.

Date of Consent (MM/DD/YYYY):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Participant (Printed): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature of Participant:

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Person who obtained consent (Printed):\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature of Person who obtained consent: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Primary Investigator (Printed): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature of Primary Investigator: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Please check one of the boxes below to indicate whether you would be willing to be contacted to participate in future research:

⬜ *Yes, I would be willing to be contacted to participate in future research.*

*I prefer to be contacted through this email address: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_*

*I prefer to be contacted through this mailing address: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_*

⬜ *No, I do not wish to be contacted to participate in future research.*

Please check one of the boxes below to indicate whether and how (if applicable) you would like a brief summary of your results after the study is complete:

⬜ *Yes, I would like to receive a summary of the study’s results.*

*I prefer it to be sent to this email address: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_*

*I prefer it to be sent to this mailing address: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_*

⬜ *No, I do not want to receive a summary of the study’s results.*

**APPENDIX C – Data Collection Form**

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**APPENDIX D – Raw Data**

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