ANKLE-BRACHIAL INDEX AND CARDIO-ANKLE VASCULAR INDEX AND THEIR ASSOCIATION WITH CARDIORESPIRATORY FITNESS AND LEISURE-TIME PHYSICAL ACTIVITY IN MEN WITH TYPE 1 DIABETES

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ABSTRACT

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Introduction. In individuals with type 1 diabetes the risk of arterial diseases is considerably increased compared to nondiabetic individuals. Since physical activity has been shown to be associated with decreased cardiovascular disease risk it could help in the management of the disease risk. The aim of this study was to compare ankle-brachial index (ABI) and cardio-ankle vascular index (CAVI) in young men with and without type 1 diabetes and to analyze the associations of ABI and CAVI with cardiorespiratory fitness and leisure-time physical activity (LTPA).

Methods. The data are a part of an "Exercise, Diet and Genes in T1D" (EDGE) Helsinki project. Twelve men with type 1 diabetes (T1D) and 17 healthy age- and anthropometry-matched men (control) volunteered in the study. All subjects performed incremental cycling exercise test until volitional fatigue to determine maximal oxygen uptake (VO_{2max}). Leisure-time physical activity was assessed through a questionnaire. ABI, CAVI, and blood pressure were measured with VaSera VS-1500.

Results. VO_{2max} was significantly lower in T1D compared to control group ($p<0.05$). No differences were found in LTPA. CAVI was significantly higher in T1D ($p<0.01$) but no difference in ABI was found. LTPA correlated negatively with CAVI in T1D ($r=-0.72$ for right and $r=-0.68$ for left CAVI, $p<0.05$) but not in control group. VO_{2max} was not found to be correlated with ABI and CAVI in T1D or control group.

Conclusions. Young men with type 1 diabetes seem to already have subclinically increased arterial stiffness possibly implicating increased risk of premature arterial stiffening and arterial complications. Cardiorespiratory fitness does not seem to be associated with arterial stiffness but increasing LTPA might be especially beneficial for individuals with type 1 diabetes to combat arterial stiffening.

Key words: type 1 diabetes, arterial stiffness, leisure-time physical activity

TIIVISTELMÄ

Iisa Alho (2017). Nilkka-olkavarsipainesuhteen ja verisuonten jäykkyyden yhteys hengitys- ja verenkiertoelimistön kuntoon sekä vapaa-ajan fyysiseen aktiivisuuteen tyypin 1 diabetesta sairastavilla miehillä. Liikuntatieteellinen tiedekunta, Jyväskylän ylipoisto, pro gradu -tutkielma, 103 s.

Johdanto. Tyypin 1 diabetesta sairastavilla valtimosairauksien riski on huomattavasti kohonnut verrattuna henkilöihin, joilla ei ole diabetesta. Fyysisen aktiivisuuden on osoitettu olevan yhteydessä matalampaan sydän- ja verisuonisairauksien riskiin, minkä takia fyysisen aktiivisuuden lisääminen voisi auttaa tyypin 1 diabeetikkojen sairastumisriskin hallitsemisessa. Tutkimuksen tarkoitus oli vertailla nilkka-olkavarsipainesuhdetta (ABI) ja valtimoiden jäykkyyttä CAVI-indeksillä mitattuna tyypin 1 diabetesta sairastavien ja terveiden nuorien miehien välillä ja tarkastella ABI:n ja CAVI:n yhteyttä hengitys- ja verenkiertoelimistön kuntoon sekä vapaa-ajan fyysiseen aktiivisuuteen (LTPA).

Menetelmät. Tässä tutkimuksessa käytetty aineisto on osa ”Exercise, Diet and Genes in T1D” (EDGE) Helsinki -projektia. 12 tyypin 1 diabetesta sairastavaa miestä (T1D) ja 17 tervettä verrokkia (kontrolliryhmä) osallistuivat tutkimukseen. Kaikki tutkittavat suorittivat polkupyöräergometritestin nousevalla kuormituksella uupumukseen asti maksimaalisen hapenottokyvyn (VO_{2max}) määrittämiseksi. Vapaa-ajan fyysistä aktiivisuutta kartoitettiin kyselylomakkeella. ABI, CAVI ja verenpaine mitattiin VaSera VS-1500 -laitteella.

Tulokset. VO_{2max} oli merkitsevästi matalampi T1D-ryhmässä kuin kontrolliryhmässä ($p<0.05$). Ryhmien välillä ei havaittu ero vapaa-ajan fyysisessä aktiivisuudessa. CAVI oli korkeampi T1D-ryhmässä ($p<0.01$), mutta ABI:ssa ei havaittu eroa ryhmien välillä. LTPA korreloi negatiivisesti CAVI:n kanssa T1D-ryhmässä ($r=-0.72$ oikea ja $r=-0.68$ vasen CAVI, $p<0.05$), mutta ei kontrolliryhmässä. VO_{2max} ei korreloinut ABI:n tai CAVI:n kanssa kummassakaan ryhmässä.

Johtopäätökset. Nuorilla tyypin 1 diabetesta sairastavilla miehillä on jo havaittavissa subkliinistä valtimoiden kovettumista, joka voisi viitata kohonneeseen ennenaikaisen valtimoiden kovettumisen ja valtimotautien riskiin. Hengitys- ja verenkiertoelimistön kunto ei näyttäisi olevan yhteydessä valtimoiden jäykkyyteen, mutta vapaa-ajan fyysisen aktiivisuuden lisääminen saattaisi olla erityisen hyödyllistä tyypin 1 diabeetikolle valtimoiden kovettumisen ehkäisemiseksi.

Avainsanat: tyypin 1 diabetes, verisuonten jäykkyys, vapaa-ajan fyysinen aktiivisuus

ABBREVIATIONS

PAD	Peripheral arterial disease
ABI	Ankle-brachial index
CAVI	Cardio-ankle vascular index
NO	Nitric oxide
CRP	C-reactive protein
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial pressure
METs	Metabolic equivalents
PWV	Pulse wave velocity
MAC	Medial artery calcification
AWV	Aortic wave velocity
CAD	Coronary artery disease
AGEs	Advanced glycation end-products
LTPA	Leisure-time physical activity

CONTENT

1 INTRODUCTION

Decreased physical activity is a major health burden throughout the world. It has been estimated that inactivity causes 9 % of the premature mortality and a decrease in the prevalence of inactivity by 10 % or 25 % could prevent more than 533 000 or 1.3 million deaths, respectively, per year worldwide (Lee et al. 2012). There is undeniable evidence that regular physical activity is effective in the primary and secondary prevention of several chronic diseases and is associated with a reduced risk of premature death (Warburton et al. 2006).

Diabetes is a complex and chronic disease that requires continuous medical care. Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality in diabetic individuals and it has the largest contribution to the direct and indirect costs of diabetes (American Diabetes Assiciation 2016). In Finland type 1 diabetes is more prevalent than in any other country (Terveyden ja hyvinvoinnin laitos 2017) emphasizing the importance of the management of diabetes, associated risk factors and related complications.

Diabetes amplifies the aging associated vascular changes that result in arterial stiffening (Zieman et al. 2005). Arterial stiffness is considered to be one of the earliest detectable manifestations of adverse structural and functional changes within the arterial wall (Cavalcante et al. 2011). Arterial stiffness is considered a marker for increased cardiovascular disease risk (Zieman et al. 2005) and is an independent predictor of coronary heart disease and stroke (Mattace-Raso et al. 2006). Leisure-time physical activity would be important in the management of the disease risk since physical activity has been shown to be associated with decreased cardiovascular disease risk (Shiroma & Lee 2010).

Ankle-brachial index (ABI) and cardio-ankle vascular index (CAVI) are noninvasive and easily performed measurements of vascular health. ABI is an indicator of atherosclerotic

process and used to diagnose peripheral arterial disease (Potier et al. 2011). CAVI represents arterial stiffness and it has been suggested as a surrogate marker of arteriosclerosis (Shirai et al. 2011). Individuals with diabetes have a greater risk of developing peripheral arterial disease compared to healthy individuals without (Marso & Hiatt 2006) and they seem to have reduced arterial compliance (Berry et al. 1999) thus the early detection of arterial changes would be especially important for this population. However, there are not many studies that have investigated the differences in ABI and CAVI in young type 1 diabetic individuals. The aim of this study was to compare ABI and CAVI in young men with and without type 1 diabetes and to analyze the associations of ABI and CAVI with cardiorespiratory fitness and leisure-time physical activity.

2 BLOOD PRESSURE AND ITS REGULATION

The circulation is divided into the systemic circulation and the pulmonary circulation. The systemic circulation supplies blood flow to all other tissues of the body than lungs and is also called the peripheral circulation. The amount of blood pumped into the aorta by the heart each minute is called cardiac output and it represents the overall blood flow in the total circulation of a person. (Hall 2011, 157–229.)

2.1 Blood pressure

The two factors that determine the blood flow through a blood vessel are pressure difference, also called pressure gradient, and vascular resistance. Pressure difference between the two ends of the vessel is the force that takes the blood through the vessel. Vascular resistance results from the friction between the flowing blood and the intravascular endothelium inside of the vessel. The velocity of the blood flow is known to be inversely proportional to vascular cross sectional area. (Hall 2011, 158–159.)

Accurately blood pressure means the force exerted by the blood against any unit area of the vessel wall and is usually measures in millimeters of mercury (mmHg) (Hall 2011, 162.) Mean aortic pressure as well as arterial systolic and diastolic pressures are related to both peripheral resistance and cardiac output. The mean arterial pressure is the product of cardiac output and peripheral vascular resistance, where cardiac output is the product of stroke volume and heart rate. Peripheral resistance is determined by contraction of smooth muscle and the radius of arteries. (Nichols & Edwards 2001.) According to Poiseuille's law, total peripheral resistance is directly proportional to blood viscosity and length of the vessel, but inversely proportional to the fourth power of the radius (Pescatello et al. 2004). This way both cardiac output and peripheral resistance can affect blood pressure.

According to the ESH and ESC guidelines (Mancia et al. 2013) blood pressure is classified as optimal if systolic pressure (SBP) is <120 mmHg and diastolic pressure (DBP) <80 mmHg, normal if SBP 120–129 mmHg and/or DBP 80 – 84 mmHg, and high normal if SBP 130–139 mmHg and/or DBP 85–89 mmHg. Hypertension is defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg. The category of blood pressure is determined by the highest blood pressure recording, whether systolic or diastolic (Mancia et al. 2013). The JNC 7 report has somewhat stricter categories by classifying blood pressure normal if SBP <120 mmHg and DBP <80 mmHg and prehypertensive if SBP 120–139 mmHg and/or DBP 80–89 mmHg, but the cut-off of hypertension is defined similarly (Chobanian et al. 2003).

2.2 The regulation of blood pressure

Blood pressure is directly related to cardiac output and peripheral resistance. Both of these are further determined by interaction of a complex series of factors (Nadar 2009a). The function of the systemic arterial tree is to deliver blood at high pressures to peripheral vascular beds. It can be divided into three anatomical regions with distinct and separate functions. The large arteries, particularly the elastic arteries including aorta, carotid, and iliac arteries, function as a buffering reservoir that stores blood during systole and ejects it to the peripheral circulation during diastole. That is, part of the energy of ventricular contraction is retained as potential energy during systole and released as kinetic energy during the systole. This way the capillaries obtain a continuous blood flow during the entire cardiac cycle. (Nichols & Edwards 2001.)

The second region is the muscular arteries, including femoral, popliteal, and posterior tibial arteries, which are about twice as long as the aorta and the iliac arteries. They regulate the travelling speed of the pressure and flow waves and determine when the reflected waves come back at the heart by modifying the tone of the smooth muscle cells. The third region, the arterioles, control peripheral resistance by altering their diameter, and that way are involved in the regulation of mean arterial blood pressure. (Nichols & Edwards 2001.) And

further, pre-capillary vessels, like arterioles and small arteries, are suggested to be the major determinant of increased vascular resistance with the diameter of a vessel mainly determining the vascular resistance (Izar et al. 2012).

The regulation of blood pressure depends on the actions of cardiovascular, neural, renal, and endocrine systems. The control of blood pressure can be divided to local, or peripheral, and central mechanisms. The peripheral mechanisms include acute and chronic vasoconstriction and dilatation, in which the endothelial autocrine secretion plays an important role, as well as change in the number and diameter of the blood vessels supplying a tissue. The central mechanisms control the blood flow, and include changes in cardiac output and regulation of arterial blood pressure through the autonomic nervous system. The most powerful chronic control mechanism of blood pressure is the integrated renal-endocrine system, which function is to balance the fluid and salt homeostasis in the body. (Chopra et al. 2011.)

2.2.1 Cardiac output

Cardiac output which is the amount of blood pumped into the aorta by the heart each minute (Hall 2011, 229) is defined as the product of stroke volume and heart rate (Nichols & Edwards 2001). Since cardiac output is directly related to blood pressure increases in the former can lead to increases in the latter. Increased cardiac output can result from increased circulating fluid volume. This can be the consequence of excess sodium intake or sodium sensitivity. If the kidneys cannot excrete this increased sodium load, salt and water retention results leading to increased circulating fluid volume and thereby to hypertension. The Renin-Angiotensin-Aldosterone System (RAAS), which is responsible for the maintenance of normal body salt and water homeostasis, plays also a major role in the development of hypertension. The function of angiotensin II is to minimize renal fluid and sodium losses to maintain blood pressure. Contrary to what would be expected, in essential hypertension the levels of renin are not suppressed but normal or even elevated leading to the development of hypertension. (Nadar 2009a.)

Increased cardiac output can also result from increased myocardial contractile force. Increases in myocardial contractile force lead to increased stroke volume and cardiac output. This way the mean arterial pressure can be elevated even without any changes in peripheral resistance. On the other hand, also increased peripheral resistance that results from contraction of smooth muscle (known as vasoconstriction) and decreased arteriolar radius can elevate mean arterial pressure alone. Thus, arterial pressure is directly connected to peripheral resistance and arteriolar diameter or tone. (Nichols & Edwards 2001.)

2.2.2 Peripheral resistance

Hyperactive sympathetic nervous system seems to be present in early hypertension. The increased activity of sympathetic nervous system resulting from the resetting of arterial baroreceptors leads to peripheral vasoconstriction and that way to elevated blood pressure. Increased peripheral resistance in the early stages of hypertension can be due to increased circulatory volume leading to compensatory peripheral vasoconstriction. With time the vasoconstriction may become permanent maintaining hypertension. Changes in endothelial function as well as in autocrine and paracrine factors play part in maintaining the increased vascular tone. (Nadar 2009a.)

One of the factors affecting contraction of smooth muscle is endothelin 1. It is secreted by endothelial cells and has very strong vasoconstrictor effect. Endothelin 1 secretion is stimulated by angiotensin II, catecholamines, growth factors, hypoxia, insulin, oxidized LDL, HDL, sheer stress and thrombin. One of the inhibitors of the secretion of endothelin 1 is nitric oxide (NO). (Chopra et al. 2011.) Accordingly, reductions in the production of NO have been found to be linked to hypertension (Nadar 2009a).

The main components of the arterial wall affecting its stiffness are elastin, collagen, and smooth muscle cells. These components are distributed differently between the central elastic arteries and the peripheral muscular arteries. An increase in stiffness associated with

changes in arterial wall composition take place over a long period of time, like with aging or hypertension. A change in the stiffness of muscular arteries is mainly the result of acute changes in smooth muscle tone. (Nichols & Edwards 2001.)

Pulse pressure and systolic pressure are directly and positively related to arterial stiffness, while diastolic pressure is directly and inversely related. This means that the stiffer the artery is the higher are systolic and pulse pressure and the lower is diastolic blood pressure. The increased systolic blood pressure results from the failure to convert kinetic energy to potential energy during ventricular contraction. That is, the stiffer the arterial wall the less potential energy they can store, leading to increased systolic pressure. As for diastolic pressure, the pressure falls because of the lack of potential energy available for reconversion to kinetic energy during diastole. This mechanism explains the lowering of diastolic blood pressure with aging while the increased reflection wave amplitude explains the elevated systolic blood pressure and decreased stroke volume associated with age-related increase in central arterial stiffness. (Nichols & Edwards 2001.)

2.3 The effects of exercise training on blood pressure

The inverse and independent relationship between physical activity, cardiorespiratory fitness, and cardiovascular and overall mortality risk is well-established (Kokkinos 2014). According to a meta-analysis, aerobic endurance training significantly reduces mean blood pressure by 4.3% and systemic vascular resistance by 7.1% (Cornelissen & Fagard 2005). In addition to the capability of moderate-intensity aerobic exercise to lower blood pressure significantly in most individuals, also dynamic resistance training seems to have a blood pressure lowering effect although acute resistance exercise has little effect on blood pressure (Pescatello et al. 2004; Brook et al. 2013). However, no significant relationship has been found between blood pressure response and characteristics of training, such as duration of training session, training frequency, intensity, and mode (Cornelissen & Fagard 2005).

The decrease in blood pressure following aerobic endurance training seems to be more pronounced in hypertensive than normotensive individuals (Pescatello et al. 2004; Fagard & Cornelissen 2007). It also appears that there is a direct relationship between the decrease in blood pressure and the increase in peak oxygen uptake. (Fagard & Cornelissen 2007.) Peak exercise capacity has also been shown to be an independent predictor of the rate of progression from prehypertension to hypertension. The relationship between progression to hypertension and exercise capacity seems to be inverse with progressively higher risk for developing hypertension with decreasing exercise capacity. However, the risk appears to be similarly increased in the least-fit (peak exercise capacity ≤ 6.5 METs) and the low-fit (peak exercise capacity 6.6–8.5 METs). The risk for developing hypertension was reported to be 72%, 66%, and 36% higher in least-fit, low-fit, and moderate fit (peak exercise capacity 8.6–10 METs) categories, respectively, compared to high-fit category (peak exercise capacity >10 METs) in middle-aged and older individuals. (Faselis et al. 2012.) It has also been demonstrated that the enhanced cardiorespiratory fitness could attenuate the blood pressure response to exercise, and thereby lower the risk for left ventricular hypertrophy (Kokkinos 2014).

Exercise is recommended as a cornerstone therapy for the prevention, treatment and control of hypertension since it contributes to the control of blood pressure in hypertensive individuals and likely also to the prevention of hypertension in normotensive subjects (Fagard & Cornelissen 2007). The decrease in blood pressure can be approximately 5–7 mmHg after an acute exercise session or following chronic exercise training. This reduction may last up to 22 hours after an endurance exercise bout. However, the extent to which the blood pressure lowering effect of endurance training is the integration or sum of the effects of acute exercise is yet unknown. (Pescatello et al. 2004.) However, the reduction in blood pressure seems to become smaller over the time after the initiation of training (Cornelissen & Fagard 2005).

An inverse dose-response relationship between recreational physical activity and incidence of hypertension has been found with both moderate-level and high-level physical activity

being associated with decreased risk of hypertension compared to low-level physical activity. However, the association between moderate-level or high-level occupational physical activity and the risk of hypertension was not different from that of low-level occupational physical activity. It needs to be taken into account that the indirect association between physical activity and decreased risk of hypertension may also be explained by the characteristics of physically active individuals who typically have an overall healthier lifestyle. (Huai et al. 2013.) An inverse relationship has also been reported between physical activity assessed by questionnaire and incidence of hypertension in young adults with fasting insulin and adiposity suggested to mediate the association (Parker et al. 2007).

Although the dose-response relationship between increased cardiorespiratory fitness, blood pressure, and mortality risk suggests causal mechanisms, the exact mechanism or mechanisms are not yet fully understood (Kokkinos 2014). Since mean arterial pressure is the product of cardiac output and total peripheral resistance the blood pressure lowering effect of endurance training must be mediated by decreases in one or both of these variables. Reductions in cardiac output do not usually occur following chronic exercise, because decreased heart rate is counterbalanced by increased stroke volume (Fagard & Cornelissen 2007), reduction of peripheral resistance seems to be the primary mechanism. Total peripheral resistance is determined by blood viscosity, the length of the vessel, and the radius of the vessel. As training does not significantly affect viscosity or the length, changes in vessel diameter would be mainly responsible for the reductions in peripheral resistance. (Pescatello et al. 2004.)

A reduction in systemic vascular resistance seems to be mediating at least partly the hypotensive effect of aerobic endurance training. This training-induced reduction in blood pressure and systemic vascular resistance may result from decreased activities of the sympathetic nervous and the renin-angiotensin systems and increased insulin sensitivity. (Fagard & Cornelissen 2007; Brook et al. 2013.) Reduction in blood pressure after aerobic training has been reported to be associated with decreases in plasma norepinephrine and plasma renin activity (Cornelissen & Fagard 2005). Possible mechanisms also include

reduced vasoconstrictor state by grater local vasodilator influence and altered vascular responsiveness to vasoactive stimuli, larger lumen diameter, and greater distensibility of the vasculature. According to studies it seems that both neural and vascular changes contribute to the reductions in blood pressure resulting from acute and chronic endurance exercise. (Pescatello et al. 2004.) Aerobic training also modifies cardiovascular risk factors resulting in reductions in body fat and abdominal visceral fat, increase in high-density lipoprotein cholesterol, and decreases in triglycerides, insulin, and glucose. (Fagard & Cornelissen 2007.) In addition, it has also been suggested that also genetics play a part in the adaptations to acute and chronic endurance exercise. (Pescatello et al. 2004.)

2.4 Hypertension

For a given cardiac output mean blood pressure is defined by the cross-sectional area and number of arterioles and arteries as they represent peripheral vascular resistance. Hypertension has traditionally been seen as the result from a reduction in the caliber and/or number of small arteries and arterioles that leads to increased peripheral vascular resistance. (London & Guerin 1999.) Hypertension is defined as persistently elevated levels of blood pressure (Perloff et al. 1993).

Hypertension is diagnosed when systolic blood pressure is ≥140 mmHg and/or diastolic blood pressure is ≥90 mmHg (Chobanian et al. 2003; Mancia et al. 2013). It is estimated that in industrialized countries about one fourth of adult population is affected by hypertension (Chopra et al. 2011). The prevalence of hypertension in general population is estimated to be about 30–45% and to rise with aging (Mancia et al. 2013). In Finland about 2 million adults have hypertension and only every fifth has an ideal blood pressure. Usually blood pressure rises with aging and it is affected by genetic factors and lifestyle. Most important lifestyle risk factors are excessive sodium intake, alcohol consumption, low physical activity, and overweight. (Käypä hoito 2014.)

Both systolic and diastolic blood pressure increases progressively during adolescence and adult life (Palatini et al. 2011). This is best explained by an increase in peripheral vascular resistance, whereas after that large artery stiffness seems to predominantly explain the changes in blood pressure. (Franklin 2008). After the age of 60–65 years there is typically increase only in the systolic component while the diastolic remains stable or even decreases leading to progressive increase in pulse pressure. This increase is considered as a possible marker of endothelial dysfunction. (Palatini et al. 2011.)

Majority of the individuals with hypertension do not have only high blood pressure but also additional cardiovascular risk factors. This should be taken into account in the management of hypertension because when present together, hypertension and other cardiovascular risk factors may be potentiated leading to a greater total cardiovascular risk than the sum of the individual components. (Mancia et al. 2013.) Typically persons with hypertension do not have any signs or symptoms indicating the presence of the disease (Siu et al. 2015).

Hypertension can be categorized as primary or essential hypertension and secondary hypertension. In secondary hypertension, usually a well-defined cause, like hyperaldosteronism or renal artery stenosis, is found to be behind the elevated blood pressure whereas in essential hypertension no obvious cause can be found. Most individuals with high blood pressure have essential hypertension. (Nadar 2009a.) The rate of progression from prehypertension to hypertension is increased by age, BMI, systolic blood pressure, and diabetes. The risk for progression to hypertension is increased by 19.5% for every 10 years of age, 16% for every 10 mmHg increase in resting systolic blood pressure, and 15% for every 5 unit increase in BMI (Faselis et al. 2012).

2.4.1 Mechanisms behind hypertension

Hypertension can result from increased cardiac output and/or increased peripheral vascular resistance. Cardiac output may be increased due to left ventricular factors like elevated heart

rate or left ventricular contractility resulting from increased activity of sympathetic nervous system. Increased peripheral resistance results from humoral factors, angiotensin and catecholamines, symphatetic nervous system, and stiffening of the arteries. (Cruickshank 2013, 8.) Hypertension induces increased wall stress, which activates the vascular smooth muscle cells and then leads to changes in the structure, morphology, mechanical properties, and contractility of the arterial wall (Hyashi et al. 2015).

The primary cause of the increased systolic blood pressure in individuals with cardiovascular diseases, including hypertension, is the increased stiffness of the central elastic arteries which results from degeneration and hyperplasia of the arterial wall. As the stiffness increases the transmission velocity of both forward and reflected, or backward, wave also increases. This induces earlier arrival of the reflected wave in the central aorta raising the blood pressure in late systole. An increase in systolic pressure also increases the stress of the arterial wall contributing to fatigue and the development of atherosclerosis. Hypertension is associated with increased arterial stiffness and pulse wave velocity which lead to changes in ascending aortic pressure. (Nichols & Edwards 2001.) Additionally, aging associated stiffening of the large elastic arteries results at least partly from functional alterations of vascular smooth muscle tone and structural changes in the arterial wall (Lessiani et al. 2016).

Endothelial activation and dysfunction are both cause and effect of hypertension. The activation of endothelium may result from different causes including diabetes, smoking or hyperlipidemia or from elevated blood pressure itself. The activation leads to changes within endothelium itself and further maintains the elevated blood pressure. Changes in nitric oxide (NO) characterize the activated and subsequent dysfunctional endothelium. Nitric oxide, which is produced by endothelium, acts to decrease vascular tone. Damage to the endothelium leads to reduction in the production of NO and to decreased endothelium-dependent vasodilatation contributing to continuance of hypertension. Other changes in the endothelium associated with hypertension are decreases in some other vasodilators

including bradykinins and prostacyclins and increase in endothelins, which act as vasoconstrictors. (Nadar 2009a.)

There is also evidence of increased adrenergic activity in patients with hypertension. Potential mechanisms behind the increased sympathetic activity associated with hypertension include increased adrenergic activity resulting from disturbed peripheral regulatory mechanisms (arterial baroreceptors, cardiopulmonary mechanoreceptors, and chemoreceptors) and a primary increase of sympathetic activity within the central nervous system. It seems likely that both genetic and environmental factors are associated with these abnormal central and peripheral mechanisms. (Palatini et al. 2011.)

2.4.2 Consequences of hypertension

Systolic and diastolic blood pressures are closely correlated with each other and are associated with cardiovascular disease risk, independently and in combination (Perloff et al. 1993). Blood pressure has a continuous and consistent relationship with cardiovascular events independent of other risk factors. The risk of myocardial infarction, stroke, renal failure, and death is the greater the higher blood pressure is. (Chobanian et al. 2003.) If not recognized early and treated appropriately hypertension ultimately leads to serious events such as myocardial infarction, stroke, renal failure, and death (James et al. 2014).

Hypertension is an independent risk factor for coronary artery disease, cerebrovascular disease, peripheral arterial disease, and heart failure. Hypertension typically occurs together with other metabolic risk factors, such as dyslipidemia, impaired glucose tolerance, and abdominal obesity. Hypertension is a significant factor in the process of atherogenesis. Cardiovascular disease risk increases in relation to the rise in blood pressure. Hypertension also plays part in the development of left ventricular hypertrophy and progression of heart failure. (Nambiar 2009.) The relationship between systolic hypertension and aortic

degeneration seems to be two-way: systolic hypertension may be the result of aortic degeneration, but it may as well accelerate aortic degeneration (O'Rourke et al. 2001).

High blood pressure also affects specific organ groups leading to the development of hypertensive target organ damage. Target organ damage includes microvascular effects, retinopathy, nephropathy, and vascular dementia, and macrovascular effects, stroke and myocardial infarctions. (Nadar 2009b.) Hypertension is known to be linked to increased all-cause and cardiovascular disease mortality, stroke, coronary heart disease, heart failure, peripheral arterial disease, and renal insufficiency (Pescatello et al. 2004).

3 PULSE WAVE AND ARTERIAL STIFFNESS

The arterial system has two main functions. First, arteries have a conduit function to deliver an adequate supply of blood to tissues and organs. The second function is to transform the pulsatile flow generated by contraction of the ventricles into a continuous blood flow in the periphery, the second function being complementary to the first one. (London & Guerin 1999.) To transform the pulsatile and periodic blood flow into continuous one, the aorta expands during ventricular systole and stores energy to be released during diastole. This enables a continuous blood flow into the peripheral circulation. (Izar et al. 2012.)

The aortic systolic distension generates a wave which propagates through the aorta and its branches. This wave is called the pulse wave. (Izar et al. 2012.) The central arterial pulse wave consists of a forward travelling wave, generated by the ejection of the heart, and a later arriving wave that is reflected from the periphery (Gordin & Groop 2012).

3.1 Central arterial pulse wave

At the onset of systole, the heart generates a forward travelling wave into the arterial tree by ejecting a volume of blood into the circulation at a given pressure. When this wave is reflected at sites of impedance mismatch, for example at branching of arteries and when approaching microvascular beds, it returns to the heart and augments the forward wave as it passes through the arterial tree. The characteristics of the reflected wave, its amplitude, and the timing of return are determined by pulse wave velocity, the distance and distribution of the reflection points from the heart, and the extent of the reflections generated at each point of reflection. (Van Bortel et al. 2010.)

The forward travelling wave is affected by ventricular ejection as well as mechanical properties of the aorta and other large elastic arteries that serve to buffer the pressure

changes. The reflected or backward wave is affected by the elastic properties of the entire arterial system, including both elastic and muscular arteries. Also the amplitude of the incident wave and the balance of vasoconstriction and vasodilatation in the peripheral circulation have an effect of the reflected wave. (Franklin 2008.) The forward and backward waves are presented in figure 1 together with the resulting pulse wave.

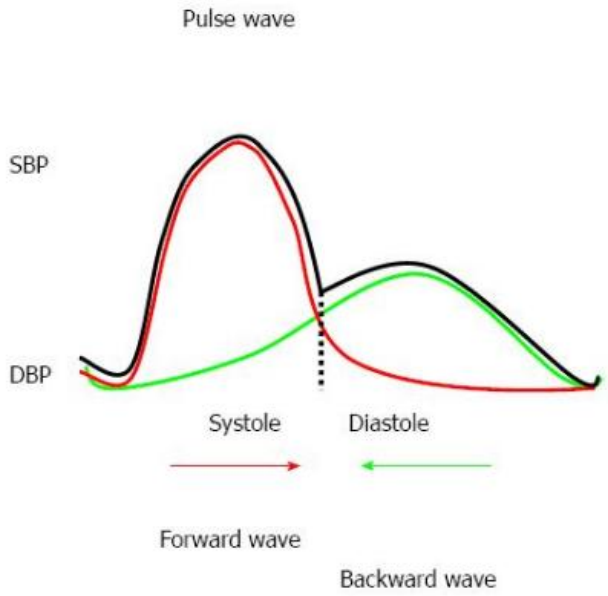

Figure 1. The arterial pulse wave.
SBP = systolic blood pressure, DBP = diastolic blood pressure (Modified from Zanoli et al. 2015.)

In young people the reflected pressure waves reach the heart in diastole resulting in increased diastolic blood pressure that assists coronary perfusion. In the presence of arteriosclerosis the reflected waves reach the heart already in the late systole because of increased pulse wave velocity in the stiffened arteries. This increased systolic blood pressure caused by early wave reflection is known as augmentation. Augmentation of the central systolic pressure increases the workload of the cardiac muscle and the concurrent fall in diastolic blood pressure reduces coronary perfusion. (Brooks et al 1999.) Augmentation increases progressively during adult life. Aging leads to gradual increase in

aortic pulse wave velocity and the return of wave reflection from the trunk and lower body progressively takes place earlier. (O'Rourke et al. 2001.)

The central and peripheral pulse waves behave somewhat differently with aging. In children the radial pulse wave contour demonstrates multiple prominent fluctuations that become less distinct with advancing age accompanied by progressive broadening of the systolic peak. In the carotid wave a second systolic peak emerges with aging, merges with and begins to dominate the initial wave after the third decade. Also the femoral pulse contours show a progressive rise in the systolic wave, leading to increased pulse pressure, and loss of any diastolic wave (Figure 2). Because the late peak is added to the initial pressure rise in the carotid artery, the increase in carotid pulse pressure is greater than the increases in the peripheral pulse pressures. (Kelly et al. 1989.)

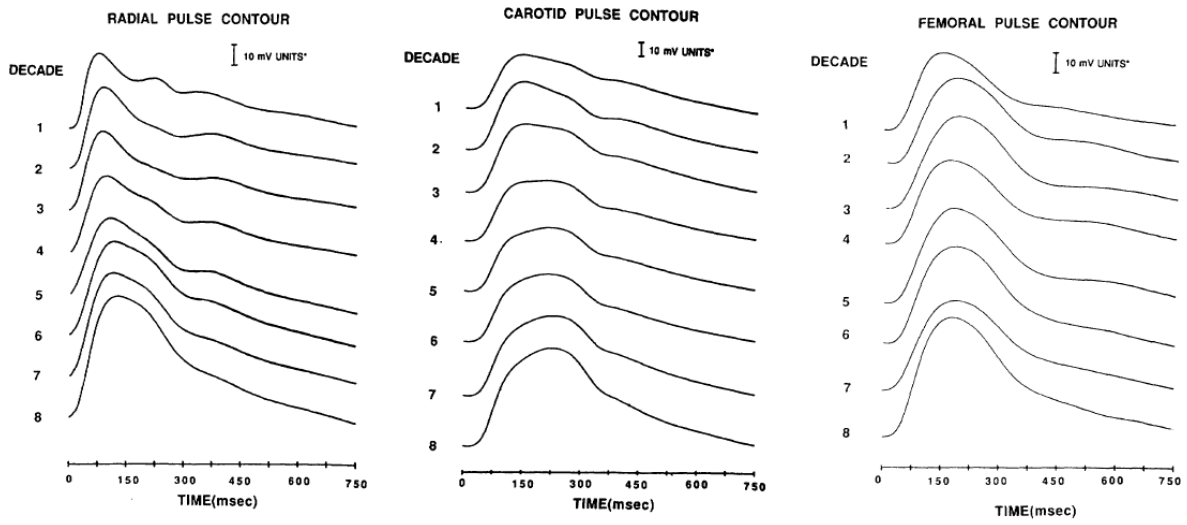

Figure 2. Contours showing averaged radial, carotid, and femoral waves. Pulse contours are displayed above each other from first decade (1) to eighth decade (8). *Amplitude is expressed in mV units. (Modified from Kelly et al. 1989.)

Changes in pulse contours can be caused by changes in the systemic vasculature itself or by alterations in flow input from the heart. It appears that the former mainly explains the changes in wave contours since there seems to be only few changes in flow input into the vasculature. The faster return of wave reflection from the lower body results in the rise in the late systolic peak found in the radial and carotid pulses. It seems that both increased aortic stiffness and increased early wave reflection contribute to the age-related increase in left ventricular pressure load. It should be noted that the increases in radial and femoral systolic pressures likely underestimate the age-related increase in central systolic pressure because the characteristic rise in the late systolic peak seen in the central arteries of mature adults is not present in peripheral arteries. (Kelly et al. 1989.)

According to a study by Karamanoglu et al. (1994) using a multibranched model of the human arterial system reflected pressure waves originating from the lower limbs do not reach the aorta since these waves do not propagate beyond the iliac bifurcation. Reflections from the upper limbs cross the ascending aorta and spread into the rest of the circulation but with considerably reduced amplitude. The reflected waves originating from the trunk, however, can travel into the central aorta as well as upper and lower limbs without considerable changes in amplitude, and thus seem to have the most pronounced effect on the central arterial waveform and ascending aortic impedance. (Karamanoglu et al. 1994.) This is supported by the data of Murgo et al. (1980) indicating that the region of the terminal abdominal aorta acts as the major reflection site in adults. Also Van Bortel et al. (2010) came to a conclusion that it is more likely pressure reflections from sites more proximal to the heart have a great impact on central pressure augmentation. This is because in order to contribute to an increased systolic central pressure, reflected waves should arrive during early systole. Considering the distance between the lower legs and the heart with realistic pulse wav velocities it seems questionable if reflected waves from these sites are able to return during early systole and augment the pressure peak. (Van Bortel et al. 2010.)

3.2 Arterial stiffness

To maintain a steady blood flow and to ensure efficient metabolic exchange a constant pressure head represented by mean blood pressure is essential. The efficiency of the ability of the arteries to transform the pulsatile flow into continuous one is determined by the viscoelastic properties of arterial wall. To perform this function arteries store part of the stroke volume during systole and eject it during diastole. This phenomenon is also familiar as "Windkessel function". (London & Guerin 1999.) Arterial compliance, which is the change in arterial volume per unit of pressure, reflects this buffering capacity of the arterial wall and depends on arterial stiffness and diameter of the vessel. Arterial distensibility is the opposite of arterial stiffness, and it is defined as the relative change in volume per unit of pressure. (Palatini et al. 2011.)

Normally about 40 % of stroke volume is forwarded directly to peripheral tissues during systole while about 60 % is stored in the aorta and major arteries (figure 3). Under conditions of decreased arterial distensibility a smaller proportion of stroke volume can be stored in the capacitive arteries thus a greater proportion of stroke volume is going directly to peripheral circulation (figure 4). This results in increased amplitude of the arterial pulse wave and increased systolic blood pressure. For a given vascular resistance increased arterial stiffness will also lead to greater fall in diastolic blood pressure. In contrast, when there is increased total peripheral resistance systolic run-off is decreased to about 30 % or less of stroke volume and a much greater proportion is stored in the capacitive arteries leading to increased diastolic run-off and elevated mean blood pressure and pulse pressure (figure 5). Since arterial stiffening increases the pulse wave velocity it may be responsible for an earlier return of reflected waves. That is, the reflected waves may return already during systole rather than during diastole and that way augment the forward travelling wave contributing further to the increase in systolic blood pressure (figure 6). In addition to increasing systolic blood pressure early return of reflected waves increases left ventricular afterload ultimately affecting cardiac function. (London & Guerin 1999.)

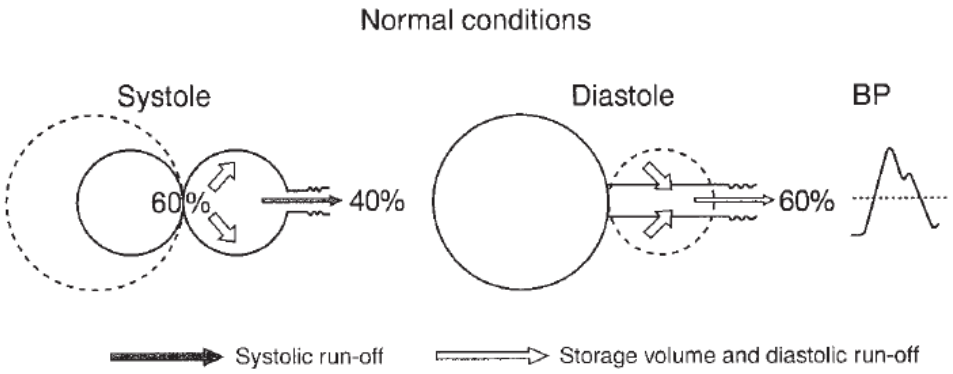

Figure 3. Diagrammatic representation of the cushioning effect of arteries in normal conditions. BP = blood pressure (London & Guerin 1999.)

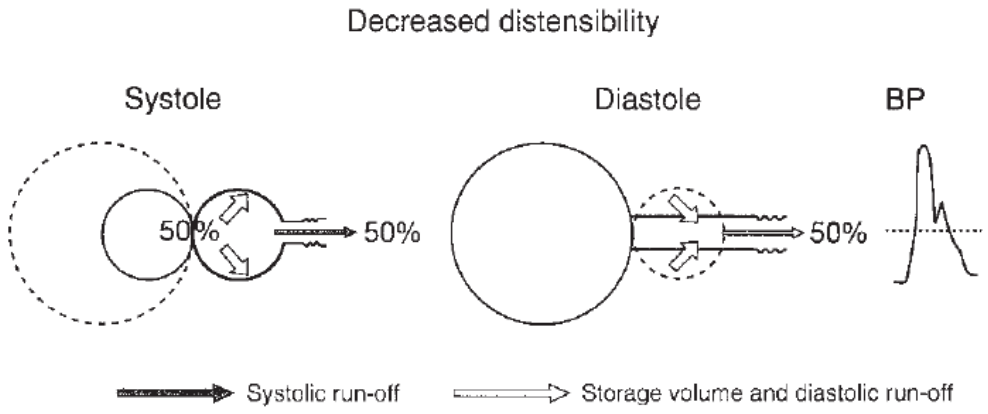

Figure 4. Diagrammatic representation of the cushioning effect in arteries with decreased distensibility. BP = blood pressure (London & Guerin 1999.)

A stiff aorta has increased impedance and does not dilate well under pressure leading stroke volume to impact directly on the arterioles (Palatini et al. 2011). That is, when the dampening function of the large elastic arteries progressively declines as happens with aging, pressure pulsatility increasingly moves towards the microvasculature. This may cause extra risk for high-flow organs such as the brain and the kidneys. In order to protect organs

from damage, the microvasculature accommodates to this increased pulsatility by means of structural changes, including increase of myogenic tone and microvascular remodeling. This in turn increases mean arterial pressure and indirectly further arterial stiffness. (Van Bortel et al. 2010.)

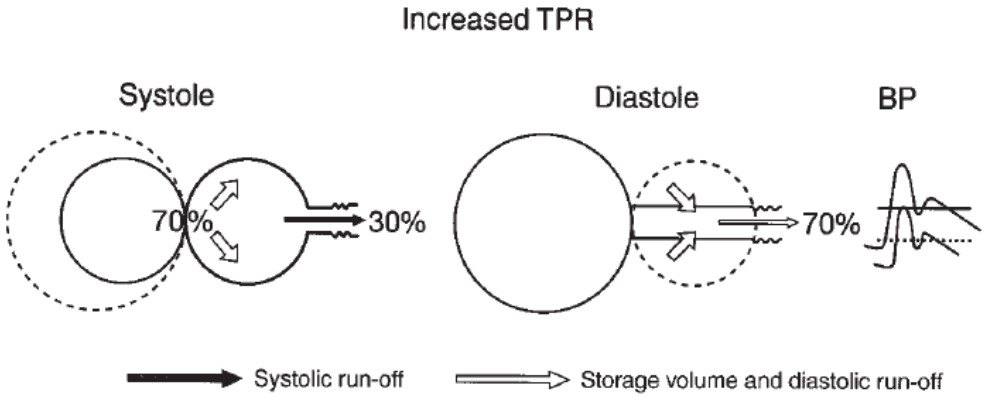

Figure 5. Diagrammatic representation of the cushioning effect of arteries when total peripheral resistance is increased. BP = blood pressure, TPR = total peripheral resistance (London & Guerin 1999.)

Increased arterial pulse pressure resulting from arterial stiffening can greatly influence blood vessel and heart biology. Arterial stiffening affects the load imposed on the ventricles, the efficiency of cardiac ejection, and the perfusion of the heart itself. That is, a higher end-systolic pressure is needed for the same net stroke volume when the heart ejects into a stiffer arterial system. Chronic elevation of mean blood pressure results in thickening of the arterial wall which is mainly present in media. Remodeling in the arterial wall associated with hypertension is a compensatory mechanism aiming to normalize increased wall stress. (Zieman et al. 2005.)

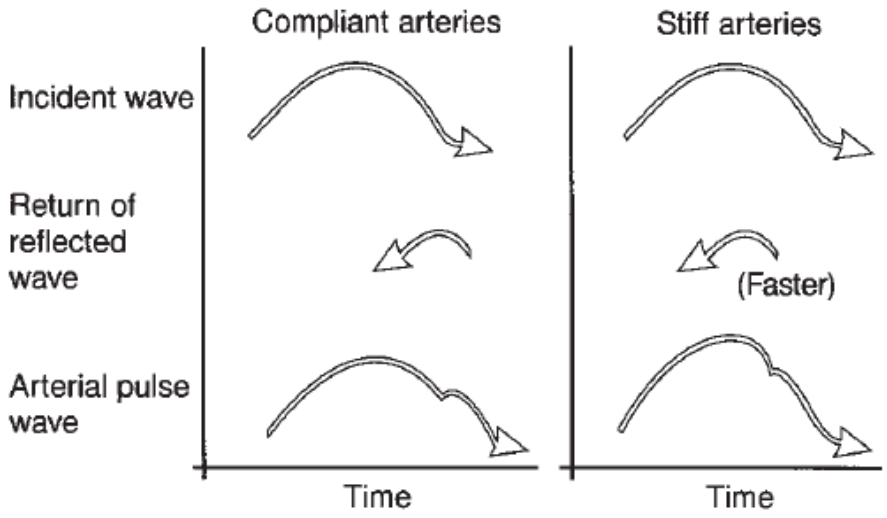

Figure 6. The effect of arterial stiffness on the timing of wave reflections and the arterial pulse wave. (London & Guerin 1999.)

Arterial stiffness is recognized as a predictor of cardiovascular morbidity and mortality and it is positively associated with the leading causes of mortality in developed countries which include systolic hypertension, coronary artery disease, stroke, and heart failure. There is a vicious circle between coronary atherosclerosis and the pulsatile component of blood pressure: diffuse atherosclerotic plaque impairs the elastic properties of the arterial wall, while increased arterial stiffness enhances pulse pressure, resulting in progression of atherosclerotic lesions. (Palatini et al. 2011.) Weber et al. (2004) have shown that noninvasive markers of arterial stiffness and wave reflection (including augmentation pressure and augmentation index) are significantly and independently associated with coronary artery disease (CAD) in young and middle-aged males. In the group of older than 60 years of age augmentation index and augmentation pressure were high in virtually all subjects, probably explaining why there were no differences in these markers between subjects with or without CAD in this group. (Weber et al. 2004.)

3.2.1 Arterial stiffness and the arterial wall

The main components of extracellular matrix in large arteries are the proteins elastin and collagen (Wagenseil & Mecham 2012). The role of elastin and collagen is to provide structural integrity and elasticity. The relative content of elastin and collagen in the vascular wall is normally held stable by a slow, but dynamic alternation of production and degradation. (Zieman et al. 2005.) Elastin-containing central arteries, the thoracic aorta and its most proximal branches, are primarily responsible for the dampening of flow pulsatility in a youthful arterial system (Franklin 2008). Stiffening of the arteries leads to situation where more pressure is needed to distend the arterial wall. Thus, increased arterial stiffness starts a negative feedback loop leading to increased mechanical load on the heart and risk of heart failure. (Wagenseil & Mecham 2012.)

The functional and structural modifications of the arterial wall affect the cardiovascular system by increasing the incidence of fracture, rupture, and aneurysm formation in arteries, potentially also contributing to the development of atherosclerosis. It is important to note that in addition to being the result of arterial stiffening, the increased systolic and pulse pressures increase the fatigue of arterial walls, further accelerating the arterial wall damage, and thus, feeding a vicious circle. It is generally accepted that increased stiffness of the large arteries associated with hypertension is caused by several structural changes in the arterial wall that include hypertrophy and alterations in the extracellular matrix, an increase in collagen being the most significant. (London & Guerin 1999.)

When the elastic lamellae become fragmented and discontinuous as a result of normal aging process the mechanical load transfers to collagen fibers that are 100–1000 times stiffer than elastic fibers. It has been found that in adult animals the elastic fibers damaged during aging or as a result of tissue injury are usually not replaced because elastin expression is turned off. Instead, the amount of elastin compared to collagen decreases when more collagen is produced to replace the damaged elastic fibers. This shifts the mechanical properties of

arteries into the stiffer range of collagen fibers. Stiffening of the arterial wall may also result from calcification of elastic lamellae and additional crosslinking by advanced glycation end-products (AGEs) that cause protein-protein crosslinks throughout the collagen molecule. (Wagenseil & Mecham 2012.) AGE-linked collagen is stiffer than normal and less sensitive to experience hydrolytic turnover (Zieman et al. 2005). AGEs are accumulated slowly with normal aging and the rate of accumulation is increased in diabetes. Thickening of the arterial wall alone can also increase arterial stiffness. (Wagenseil & Mecham 2012.) In addition, endothelial cell signaling and vascular smooth muscle cell tone play a major part in arterial stiffness. The multiple causes and locations of arterial stiffness are presented in figure 7. (Zieman et al. 2005.)

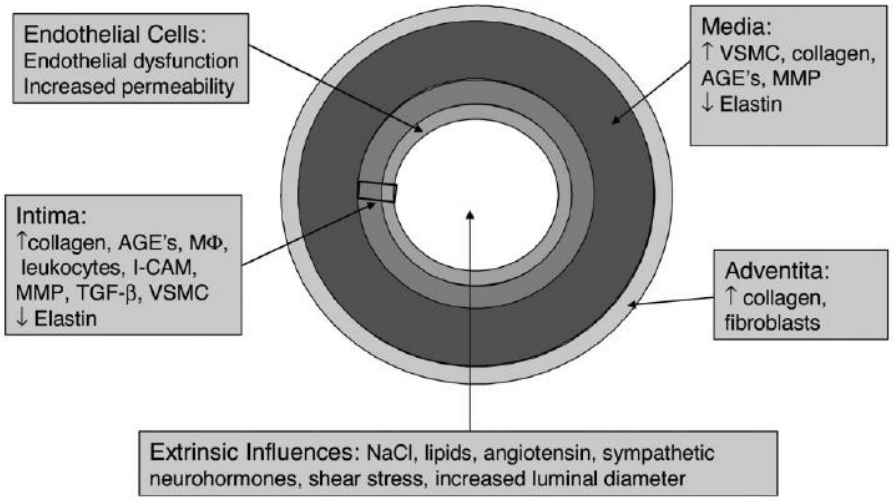

Figure 7. Summary of the causes and locations of arterial stiffness. (Zieman et al. 2005.)
I-CAM = intracellular adhesion molecule, MMP = matrix metalloprotease, TGF-β = transforming growth factor β, VSMS = vascular smooth muscle cell, AGEs = advanced glycation end products

Endothelial dysfunction, which is characterized by a reduced bioavailability of endothelium-derived NO, is recognized as a step in the progression of atherosclerosis. It has been suggested that endothelium derived NO might contribute also to the regulation of large artery stiffness. McEniery et al. (2006) have found that there is a stronger correlation

between global endothelial function and central rather than peripheral pulse pressure. They also reported that endothelial function is independently and inversely correlated with aortic PWV and augmentation index indicating that as endothelial function declines, the aortic PWV and augmentation increases. These results suggest endothelial function to be an important determinant of central hemodynamics and large artery stiffness and that NO has an important role the regulation of large artery stiffness. (McEniery et al. 2006.) However, the association between endothelial dysfunction arterial stiffening is two-way: endothelial dysfunction plays part in vascular stiffening but structural stiffening may also alter endothelial function and thereby increase stiffening. The ability of the vessel wall to stretch seems to be important also because the lack of compliance may promote a decline in nitric oxide synthase activity, which further increases arterial stiffness (Zieman et al. 2005.)

The level of sympathetic nervous activity seems to be involved in determining properties of large arteries and short-term sympathetic activation is also capable of reducing radial arterial compliance. The association between increased sympathetic activity and arterial function is further supported by the observation that pathological states characterized by sympathetic nervous system activation are associated with arterial stiffness. For instance, sympathetic overactivity has been linked with the development and progression of hypertension and its complications. (Palatini et al. 2011.)

There may be several mechanisms linking autonomic nervous system activity and arterial stiffness. Sympathetic nervous system contributes to endothelial dysfunction, growth of vascular muscle and associated fibrosis, promoting structural changes of arterial wall. Sympathetic nervous system can also affect the renin-angiotensin aldosterone system increasing arterial stiffness by promoting arterial wall fibrosis. Also the loss of large vessel elasticity resulting from increased sympathetic activity may facilitate the transmission of pressure stress into the resistant vessels and microvasculature. Resetting of the baroreflex that results from sympathetic overactivity and structural changes may additionally promote target organ damage. (Palatini et al. 2011.) Considering the association between atherosclerosis and arterial stiffening, the pathophysiology of atherosclerosis involves many

similar processes that can lead to vessel remodeling and altered collagen and elastin structure, but it remains uncertain whether the deposition of lipids in the vascular wall and development of atherosclerotic lesions alone have an impact on vascular stiffness (Zieman et al. 2005.)

3.2.2 Pulse pressure

The traditional view sees mean arterial blood pressure as a constant throughout the cardiac cycle but the pulsatile nature on blood pressure may be forgotten about. (London & Guerin 1999.) The arterial pulse wave has both a pulsatile component represented by pulse pressure and a steady component represented by mean arterial pressure. Pulse pressure is determined by cardiac output, heart rate, large artery stiffness, and early wave reflection, and represents pulsatile opposition to blood flow during systole. It is the difference between peak systolic and end diastolic blood pressure. In contrast, mean arterial pressure is determined by cardiac output and peripheral vascular resistance in the absence of pulsations. It is calculated from the standard equation of MAP = (2/3)DBP + (1/3)SBP. It should also be noted that brachial pulse pressure may not be as reliable marker of cardiovascular risk as central pulse pressure because the heart, brain, and kidneys are affected by aortic pressure rather than brachial pressure. (Franklin 2008.)

The height of the first systolic shoulder in the arterial pulse wave and augmentation pressure are considered to be the two main components of central pulse pressure (figure 8). The height of the first systolic shoulder is determined by the outgoing pressure wave and depends on stroke volume as wells as arterial stiffness. Augmentation pressure depends mainly on pressure wave reflection, and thus, on the serial distribution of arterial dimensions and arterial stiffness. It seems that increased wave reflection rather than PWV is the main determinant of increased pulse pressure in women. The mismatch in distal-to-proximal arterial dimension seems to play key part in this, especially in younger women under the age of 60. (Cecelja et al. 2009.)

Surprisingly, in infants pulse pressure is remarkably similar to that seen in elderly subjects because the secondary diastolic wave in addition to systolic peak wave becomes apparent with bodily growth only in late adolescence. This similarity results from the early return of wave reflection from peripheral to central vessels because of the short body length in infants. In the elderly, stiffening of the aorta and high pulse wave velocity explains the earlier return of wave reflection despite normal adult body dimensions. (O'Rourke et al. 2001.) It has been shown that pulse pressure is associated with adverse cardiovascular outcomes independent of other blood pressure components (Palatini et al. 2011.)

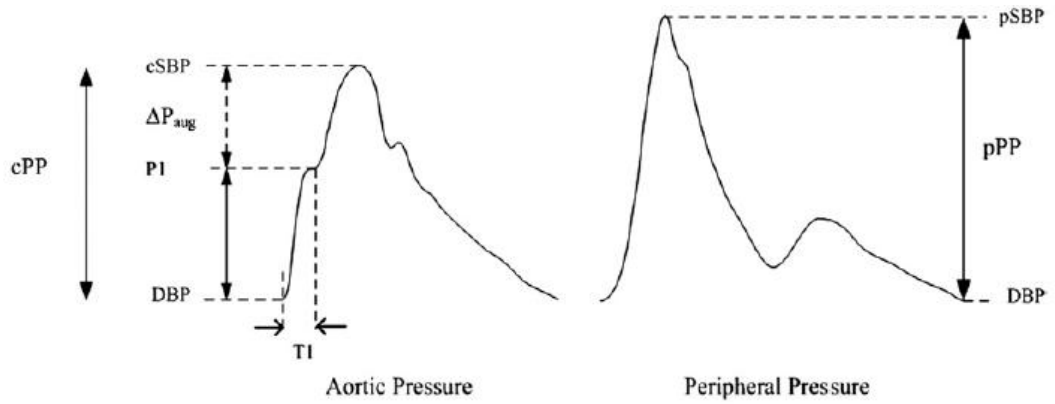

Figure 8. Aortic and peripheral pressure waveforms.
cSBP=central systolic pressure, pSBP=peripheral systolic pressure, cPP=central pulse pressure, pPP= peripheral pulse pressure, DBP=diastolic blood pressure, P1=the height of the first systolic shoulder above diastolic blood pressure, ΔP_{aug}= augmentation pressure, T1=the time of the first systolic shoulder. (Cecelja et al. 2009.)

3.2.3 Pulse wave velocity

Pulse wave velocity (PWV) is defined as the speed at which the forward pressure wave is transmitted from the aorta through the vascular tree (Gordin & Groop 2012). Pulse wave velocity depends on the effective stiffness of the artery, the timing and magnitude of reflected waves and minimally also on the inertial and viscous losses (Wagenseil &

Mecham 2012). The elastic and geometric properties of the arterial wall along with blood density have an effect on the speed of the pulse wave (Shirai et al. 2006). The idea of PWV measurement is to determine the speed of the pulse wave in a vessel. (Gordin & Groop 2012.)

PWV can be calculated using the equation: Velocity = D/T, where D represents the distance traveled by the pulse between proximal and distal recording sites, and T represents the time taken by the front wave to travel from the one site to the other (Shirai et al. 2006). PWV describes the time delay between pressure waves appearing at proximal and distal sites along the aorta (Lessiani et al. 2016). The measurement of PWV is based on the idea that the propagation of pressure wave is faster in a stiffer tube than in a softer one (Hayashi et al. 2015). However, the problem with the PWV in clinical use is that it is itself essentially dependent on blood pressure (Shirai et al. 2006).

3.3 Exercise and arterial stiffness

Physical activity has been shown to protect against stiffening of the large arteries (Gordin & Groop 2012). Poor cardiorespiratory fitness and low physical activity have been recognized as factors determining greater arterial stiffness which can also in part explain the relationship of these variables and increased cardiovascular risk. VO_{2max} has been shown to be inversely and significantly related to arterial stiffness as measured by PWV independent of lifestyle variables, body fatness, and physical activity. Also sports-related physical activity has been reported to be inversely and significantly related to PWV. This relationship was independent of lifestyle variables and body fatness but the strength of the association decreased markedly after further adjustment for VO_{2max}. Thus cardiorespiratory fitness seems to be inversely associated with arterial stiffness but only sports-related physical activities, not work or leisure physical activities, were inversely associated with arterial stiffness, an association that was mediated by cardiorespiratory fitness. These results

suggested that the beneficial effects of exercise on arterial stiffness are most likely to follow from exercise targeting improvements in $VO_{2max.}$ (Boreham et al. 2004.)

Maximal oxygen consumption is in part affected by the ability of the arterial system to dilate and thereby increase the flow to exercising muscle. There has been shown to be an inverse relationship between maximal oxygen consumption and indexes of arterial stiffness in healthy sedentary individuals. Therefore in sedentary population, differences in exercise capacity may be associated with differences in arterial stiffness. This way, arterial stiffness could also be a factor explaining differences in exercise capacity among sedentary individuals. Alternatively, differences in physical activity or other lifestyle factors may explain the heterogeneity of arterial stiffness between sedentary individuals. This is supported by the finding that in endurance trained senior male athletes the arterial stiffness indexes (AGI, APWV) has been reported to be significantly lower than in their sedentary age peers in spite of similar systolic and pulse pressure. These findings suggest that regular aerobic exercise could alleviate the age-associated increase in arterial stiffness. (Vaitkevicius et al. 1993.)

In elderly people a lower amount of light physical activity (1.1–2.9 METs) has been reported to be associated with higher arterial stiffness measured as carotid-femoral pulse wave velocity although the association was not visible in younger age groups. In subjects under the age of 40 years there was no relationship between daily time spent in physical activity and arterial stiffness. However, in middle-aged PWV was found to be negatively correlated with the daily time spent in moderate and vigorous physical activity and in the elderly negatively with light and moderate physical activity and positively with inactivity. When considering the effect of cardiorespiratory fitness, PWV was found to be negatively correlated with the daily amount of light physical activity in unfit elderly subjects while there was no association in older fit subjects. These results suggest that a longer time of light physical activity of <3 METs is related to decrease in arterial stiffening especially in unfit older people, independent of the daily amount of moderate or vigorous physical activity. (Gando et al. 2010.)

Considering the effect of exercise intervention on arterial stiffness, Lessiani et al. (2016) found that eight-week high-amount, high intensity exercise program led to significant reduction in PWV. The training program also reduced oxidative stress suggesting that the favorable effects of physical activity on endothelial function may be exerted through a reduction of oxidative stress. Additionally PWV and oxidative stress levels were found to be directly correlated throughout the study. Thus, oxidative stress might be the link between sedentary lifestyle and increased arterial stiffness. This is supported by the finding that sedentary lifestyle is associated with increased oxidative stress and oxidative stress is directly related to increased PWV. (Lessiani et al. 2016.)

A meta-analysis by Montero et al. (2015) focused on the relationship between different training modes and arterial stiffness. The analysis revealed that aerobic training decreases PWV in comparison with control groups but there was no significant difference in PWV between combined training (aerobic and resistance) and control groups. This was especially apparent in interventions with higher volumes of aerobic training the decrease in PWV was more pronounced following aerobic training than combined training. Accordingly combined aerobic and resistance training seems to have less impact on arterial stiffness compared to aerobic training only. (Montero et al. 2015.)

Hanssen et al. (2015) found in their study that the type and intensity of endurance exercise affects the acute effects on the augmentation index (AIx), a validated parameter of arterial stiffness, which represents the augmentation of systolic blood pressure by reflection of the peripheral pulse wave. They found that the AIx decreased rapidly following high intensity interval training (HIIT) bout and was lower at the end of the recovery phase compared to continuous exercise. It was proposed that NO induced dilatation would to be a key mechanism underlying the post-exercise reduction of pressure augmentation. HIIT also led to lower values during the 24-h follow-up period compared to continuous exercise suggesting a reduction in arterial stiffness. However, it is not yet known if these acute effects eventually accumulate and result in chronic training effects or are only transient. It was concluded that exercise intensity may be a crucial component for promoting favorable

effects on arterial stiffness, especially in young adults, and therefore HIIT could be an effective mean to improve arterial wave reflection, reduce arterial stiffness and myocardial burden. (Hanssen et al. 2015.)

Interestingly, although a higher aerobic fitness is associated with lower aortic wave velocity (AWV) in normotensive individuals, AWV is nearly identical in fit and unfit hypertensive individuals. This implies that the factors causing central arterial dysfunction in hypertension may not be modifiable through training. In comparison to untreated hypertensive individuals, hypertensive subjects taking antihypertensive medication have significantly lower systolic blood pressure, diastolic blood pressure, and mean arterial pressure but there seems to be no difference in AWV between these groups suggesting that these reductions in pressure are not mediated by increases in aortic distensibility. (Kraft et al. 2007.)

Because there is an inevitable increase in the aortic wave velocity with aging even among the fittest individuals without hypertension it seems likely that arterial stiffening is mediated through several processes, some of which may be reversible and some irreversible. The increased AWV associated with aging may represent the irreversible component of aortic stiffening while the higher AWV of the unfit (normotensive) individuals could be explained by reversible mechanisms of stiffening. However, the pathophysiology of hypertension may be associated with aortic stiffening that is particularly resistant to modification and therefore not affected by increased physical activity. (Kraft et al. 2007.)

4 ANKLE-BRACHIAL INDEX (ABI)

Peripheral arterial disease (PAD) is a clinical indication of atherosclerosis. The cardiovascular morbidity and mortality in individuals with PAD is from three to four fold higher compared to individuals without PAD. (Xu et al. 2010.) Although the diagnosis of PAD would be significant for prognosis since therapeutic lifestyle changes and medical therapy are needed, PAD continues to be among the least recognized and treated forms of atherosclerosis (Beckman et al. 2006). To diagnose PAD, physical examination provides important information but non-invasive testing is usually necessary to confirm the diagnosis. Since many individuals have rather atypical symptoms or are asymptomatic, classical claudication symptoms are neither reliable indicator of PAD nor adequate enough in determining individual's health status due to PAD. (Marso & Hiatt 2006.)

The ankle-brachial index, ABI, was introduced in the late 1960s. It is a simple test used to diagnose PAD in clinical and scientific fields. (Potier et al. 2011.) The ankle-brachial index is a quantitative measurement that has been found to be more accurate compared to assessment of pulses or medical history to diagnose PAD (American Diabetes Association 2003). ABI is defined as the ratio of systolic blood pressure at the ankle to that in the arm. In healthy individuals systolic pressure at the ankle is typically higher than at the arm and generally ABI <0.9 is considered to be indicative of PAD (Gornik 2009). The ABI measurement is relatively quick and easy to perform and it has been used for years in the diagnosis of PAD and in the evaluation of its severity. (Ankle Brachial Index Collaboration 2008.) ABI measurement allows detecting PAD at an early stage, even when there are no symptoms of the disease (Kaiser et al. 1999). Advantages of ABI are that it is simple, quick, and non-invasive test which can be done in an office environment by a trained physician or nurse (Stehouwer et al. 2009).

4.1 The principle of ABI

The ankle-brachial index known as ABI assesses blood flow to the ankle and serves as a marker of vascular pathology (Jelinek & Austin 2006). ABI is defined as the ratio of the ankle systolic blood pressure to the brachial systolic blood pressure (Doobay & Anand 2005). The basis of ABI measurement is presented in the figure 9. The ABI for each lower extremity is typically calculated by dividing the higher of the two ankle pressures by the higher of the two brachial artery pressures. (Cooke & Wilson 2010.)

In healthy adults with normal limb arterial circulation, ankle systolic blood pressure is typically 10–15 mmHg higher than brachial systolic blood pressure, because of the effect of pulse wave reflection (Gornik 2009). That results in a normal ABI of >1.10. Usually ABI values of <0.90 are considered a pathological threshold to define PAD and high CV risk. (Potier et al. 2011.) It has been reported that in symptomatic individuals ABI ≤0.90 is approximately 95% sensitive in detecting PAD diagnosed by arteriogram and has almost 100% specificity to identify healthy individuals (Norgren et al. 2007).

However, ABI is a continuous variable which marks the severity of the arterial occlusion and the cut-off of 0.9 is rather arbitrary. Therefore a normal but low ABI could indicate an early or moderate atherosclerotic process in the arteries of lower limbs. On the other hand also high ABI values in diabetic patients could be a sign of PAD and thus ABI values above the normal range are thought to indicate damage in cardiovascular system. (Potier et al. 2011.) A low ABI can result from a partial obstruction of any part of the vascular system from aorta to lower limb arteries, while the unusually high ABI values are considered to be indicative of non-compressible arteries (MacDougall et al. 2008).

A resting ABI of ≤0.90 results from hemodynamically significant arterial stenosis. ABI ≤0.90 is also the most often used definition of PAD. If blood pressure at the ankle is decreased in relation to blood pressure at the arm, it is an indication of the presence of

peripheral atherosclerosis. A reduced ankle blood pressure is also an independent risk factor for cardiovascular events. A low ABI is usually a sign of the presence of hemodynamically significant occlusive disease between the heart and the ankle. A low ABI strongly predicts the risk of future cardiovascular events independently of other risk factors with lower ABI predicting higher risk. (Norgren et al. 2007.)

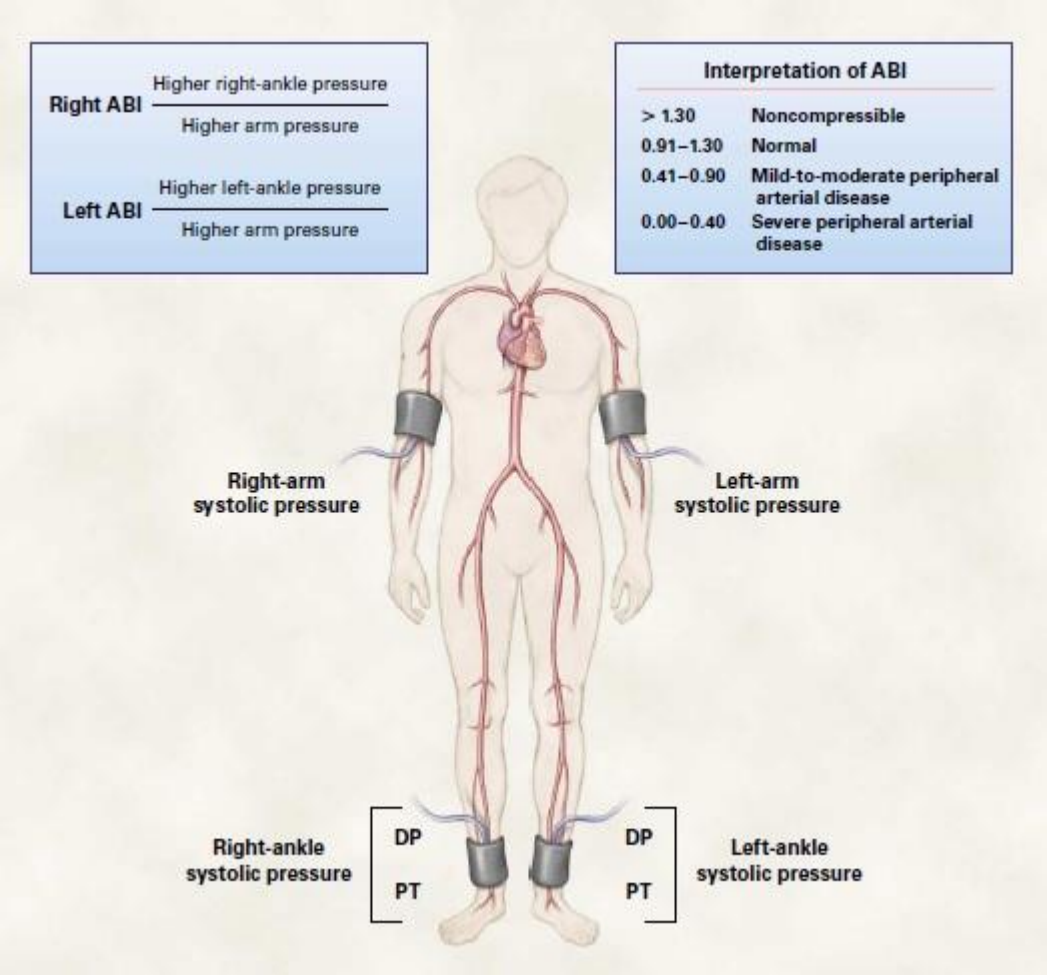

Figure 9. Measurement of ankle-brachial index (ABI), determination of right and left ABI and interpretation of ABI values (Hiatt 2001). DP=dorsalis pedis, PT=posterior tibialis.

Since ABI is a continuous variable it gives information about the severity of arterial disease and also allows comparison between patients as well as sequential measurements to monitor disease progression (Golledge 1997). In PAD the systolic blood pressure is lower at the ankle than at the arm which leads to ABI values <1.00. PAD is usually defined as an ABI <0.90 with lower values indicating more severe PAD and higher cardiovascular risk. (Marso & Hiatt 2006.) ABI values of 0.91–1.30 are considered normal, whereas values between 0.70 and 0.90 indicate mild occlusion, 0.40–0.69 moderate occlusion, <0.40 severe occlusion and values over 1.30 poorly compressible vessels. (Potier et al. 2011.) According to Ankle Brachial Index Collaboration (2008) an ABI between 1.11–1.40 can be considered normal in both men and women because the difference in cardiovascular risk between these values has been shown to be so small. On the other hand individuals with ABI between 0.91 and 1.10 or over 1.40 had a slightly higher risk compared to normal levels. These results are consistent across a diverse spectrum of populations and despite of different ABI measurement methods. (Ankle Brachial Index Collaboration 2008.)

There are several different methods used measuring ABI. Typically ABI is measured using the Doppler method (Xu et al. 2010; Hirsch et al. 2006; Potier et al. 2011). Instead of the Doppler instrument a normal stethoscope or an automatic blood pressure device used normally at the arm can be used in measuring of ABI. (Potier et al. 2011.) Other methods reported in research articles include auscultatory-ABI, palpation-ABI, photoplethysmography and exercise ABI (Xu et al. 2010).

4.2 ABI and cardiovascular risk factors

The association between peripheral arterial disease and cardiovascular disease (CVD), future cardiovascular events, and total mortality is well established (Criqui et al. 2008). There association between an abnormal ABI and increased risk of coronary heart disease mortality and morbidity has also been found to be strong (Marso & Hiatt 2006). In addition to the independent association of very low and low ABI (<0.70 and 0.70 ≤ ABI <0.90

respectively) with an increased risk of all-cause mortality, CVD mortality, and combined CVD morbidity/mortality there is also an association between high ABI values (≥1.40) and increased cardiovascular event risk. Also a decrease in ABI of more than 0.15 between two visits is shown to be associated with a significantly higher risk of cardiovascular events independent of the time between the visits, the severity of PAD, and traditional CVD risk factors. (Criqui et al. 2008.)

ABI measures the severity of PAD and therefore has a strong correlation with mortality. A nearly linear relationship has been suggested between ABI and cardiovascular events in which each decrease in ABI of 0.10 is related to a 10% increase in relative risk for a major vascular event. ABI also correlates with carotid intimal thickness. Individuals with elevated ABI seem to have similarly increased mortality risk as individuals with low ABI. An ABI ≤0.90 has been shown to be associated with a 3–6-fold increased risk of cardiovascular mortality. (Norgren et al. 2007.) Therefore it does not seem surprising that history of cardiovascular disease is among the best predictors of ABI result together with pulse pressure and smoking status (Kollias et al. 2011).

4.3 ABI guidelines in detecting PAD

ABI measurement can be used to confirm the diagnosis of PAD, detect PAD in asymptomatic individuals, and predict long-term prognosis. It also provides further risk stratification and server as an aid in differential diagnosis of leg symptoms. (Norgren et al. 2007; Stehouwer et a. 2009.) ABI is recognized as the primary non-invasive screening test for PAD and it is strongly suggested that it should become a routine measurement in the primary care. (Norgren et al. 2007). ABI has also been found to provide independent risk information in addition to the Framingham risk score. A low ABI combined with the Framingham risk score approximately doubles the risk of all-cause mortality, cardiovascular mortality, and major coronary events. (Ankle Brachial Index Collaboration 2008.)

According to the recommendations of The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) ABI should be measured in 1) all individuals with exertional leg symptoms, 2) individuals between the age of 50–69 with cardiovascular risk factor, especially if diabetes or smoking, 3) all individuals ≥70 years of age, and 4) individuals with Framingham risk score of 10%–20% (Norgren et al. 2007). It has also been proposed that in primary care it would be reasonable to screen people over 70 years of age and those aged 50–69 years who have one or more cardiovascular risk factors, such as hypertension, elevated serum cholesterol, dysglycemia, smoking, or family history of atherosclerotic cardiovascular disease (Doobay & Anand 2005). Also the Guidelines for the Management of patients with Peripheral Arterial Disease state that the measurement of ABI should be considered a routine test for all individuals at risk of lower extremity PAD. It is considered appropriate in targeted risk populations, including individuals younger than 50 years of age with history of diabetes and one other risk factor, individuals 50–69 years of age with history of smoking or diabetes, individuals 70 years and older, those with an abnormal lower extremity pulses, and those with known atherosclerotic coronary, carotid, or renal artery disease. (Hirsch et al. 2006.)

4.4 ABI and physical activity

Regular leisure-time physical activity seems to protect from PAD since abnormal ABI has been found in greater proportion in nonactive than active middle-aged men (Asgeirsdottir et al. 2001). Delaney et al. (2013) reported that intentional exercise (activities consciously done for exercising) reduces the risk of incident PAD in middle-aged and older individuals. Also Kulinski et al. (2015) have shown that daily exercise time is positively associated with ABI. Among physical activity especially walking over an hour per day has been reported to protect from PAD (Ruiz Comellas et al. 2015).

Although Delaney et al. (2013) did not find an association between moderate and vigorous physical activity and progression to low ABI, may other studies have shown that the

intensity of physical activity may be important. Those with low ABI seem to have less moderate-to-vigorous physical activity and spend more time in sedentary behaviors than individuals with normal ABI. Already a small increase in physical activity seems to lower cardiovascular disease risk because every 1-minute increase in moderate-to-vigorous physical activity was found to decrease the Framingham risk score 3.4 % in individuals with low ABI. (Hawkins et al. 2013.) The relationship between moderate-to-vigorous physical activity appears to be independent of light physical activity and sedentary behavior suggesting more vigorous activities to be more protective than lighter activities against PAD (Parsons et al. 2016). However, the duration of the exercise bout (≥10 min or <10 min) does not seem to be important factor affecting the association between moderate-to-vigorous physical activity and ABI (Parsons et al. 2016).

Leisure-time physical activity is positively correlated with ABI both in healthy individuals and in individuals with PAD independent of many possible confounding factors (Ruiz Comellas et al. 2015). On the other hand, also sedentary time has an inverse association with ABI independent of physical activity (Kulinski et al. 2015). Longer bouts of sedentary behavior have not been found to be more strongly associated with ABI than shorter bouts (Parsons et al. 2016) suggesting that all sedentary time regardless of its duration is associated with lower ABI.

In patients with intermittent claudication peak oxygen uptake was significantly higher in subjects with higher ABI (mean ABI 0.81) than in subjects with lower ABI (mean ABI ≤ 0.61) (Gardner & Clancy 2006). A progressive decline in the average intensity of leisure-time physical activity was reported to occur with a decline in ABI in subjects with intermittent claudication without a difference in mean duration of physical activity. This suggests that in individuals with ABI <0.7 claudication symptoms may limit their engagement in more vigorous activities. (Gardner & Clancy 2006.)

In a meta-analysis by Parmenter et al. (2015) exercise training was not found to affect ABI in people with PAD. However, 12 week home exercise program (Oakley et al. 2017) and supervised exercise program (Mazari et al. 2012) has been reported to improve ABI in individuals with intermittent claudication due to PAD. Also Spronk et al. (2009) found improvement in ABI after hospital-based exercise program in patients with intermittent claudication. On the other hand, dynamic leg exercise twice weekly for 6 months did not improve ABI in subjects with unilateral claudication (Perkins et al. 1996).

5 CARDIO-ANKLE VASCULAR INDEX (CAVI)

In routine medical practice arteriosclerosis is not easy to diagnose. One factor noticed to accompany the progression of arteriosclerosis is arterial wall stiffness. (Saiki et al. 2016.) Different parameters have been used to evaluate arterial stiffness, PWV being among the most widely used ones as can be seen from chapter 3. However, PWV is itself dependent on blood pressure which makes it problematic in clinical use, for example to evaluate the role of hypertension on arterial stiffness (Hayashi et al. 2015).

A new concept of measuring the stiffness of the aorta, femoral artery and tibial artery as a whole was proposed by Shirai et al. (2006). They developed a new index which was named the cardio-ankle vascular index (CAVI). Theoretically CAVI is not affected by blood pressure at the time of the measurement. It is a noninvasive measurement of the properties of the arterial tree and can be used for the evaluation of arteriosclerosis. (Shirai et al. 2006.) The interest in CAVI is increasing indicated by a growing number of research papers on CAVI and its utility in clinical medicine is currently being investigated by many researchers across the world (Hayashi et al. 2015).

5.1 The principle of CAVI

CAVI links PWV with stiffness parameter β, which represents the change in blood pressure needed to expand the diameter of the artery and therefore is not dependent on blood pressure. The equation of CAVI is presented as follows: $CAVIo = \ln(Ps/Pd) \times 2\rho/\Delta P \times PWV^2$, where Ps is systolic blood pressure, Pd is diastolic blood pressure, ΔP is Ps-Pd, ρ is blood density, and PWV is pulse wave velocity from the origin of the aorta to the tibial artery et the ankle. (Shirai et al 2011a.) Blood pressure measured from the upper brachial artery has been adopted in the calculation of CAVI because it would be impossible to

measure the whole blood pressure from the origin of the aorta to the tibial artery at the ankle although the equation refers to whole blood pressure (Hayashi et al. 2015).

CAVI represents the overall stiffness of the aorta, femoral artery, and tibial artery, and therefore is fundamentally the stiffness parameter of a long segment of arterial wall (Shirai et al 2006). It is thought to reflect both the organic stiffness of the arterial wall due to collagen, elastin, and calcification and the functional stiffness resulting from smooth muscle cell contraction (Saiki et al. 2016). In theory soft and flexible arteries, which are substantially expanded by increased blood pressure, give a low CAVI whereas arteriosclerotic arteries expanding less by an increase in blood pressure give a high CAVI (Sun 2013). The cut-off point of CAVI 9.0 is used to diagnose arteriosclerosis (Shirai et al. 2011a; Kotani & Remaley 2013).

CAVI can be determined by measuring pulse wave velocity and blood pressure. The measurement itself is easy and does not need special techniques. The brachial and ankle pulse waves are instructed to be detected with the cuff pressure as low as possible, such as 30–50 mmHg, and to be measured before the measurement of blood pressure requiring much higher cuff pressures to minimize vascular stress. (Shirai et al 2006.) The measurement of CAVI is presented in figure 10. In order to obtain reliable values the temperature of measurement room should be kept at 24–26°C and vigorous exercise, smoking, and diet should be avoided 3–4 h before the measurement of CAVI (Saiki et al. 2016). In healthy individuals daily rhythm of CAVI is fundamentally not observed nor appears CAVI to be affected by heart rate itself (Hayashi et al. 2015). However, CAVI may not be a reliable marker of arterial stiffness in people with a severe arteriosclerotic femoral artery (ABI < 0.9) (Shirai et al 2006).

In addition to being theoretically not dependent of blood pressure, it has also been shown experimentally (Kubozono et al. 2007; Shirai et al. 2011b). CAVI did not change when β-1 blocker, thought to decrease blood pressure through reduced heart muscle contraction, was

administered. However, when α-1 adrenergic receptor blocker, which is supposed to decrease blood pressure by reducing vascular smooth muscle cell tone and peripheral

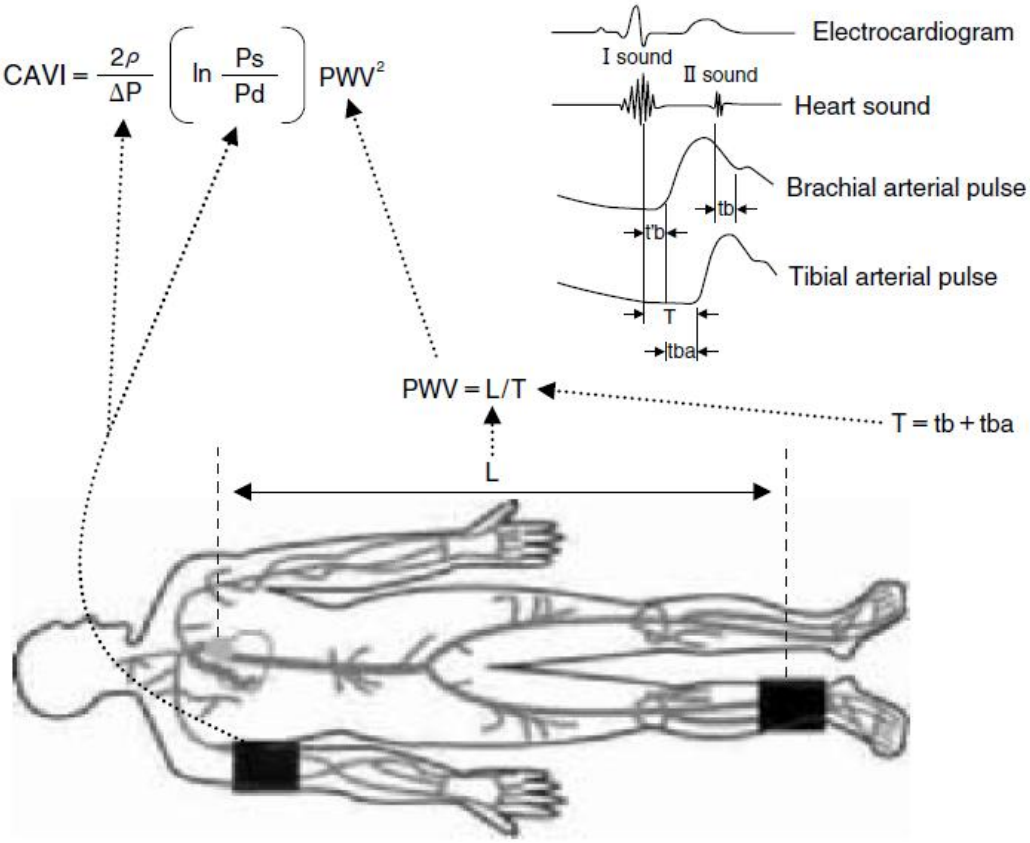

Figure 10. CAVI and its measurement.

Patients are placed supine. Electrocardiogram and heart sounds are monitored. PWV from the heart to the ankle is obtained by measuring the length from the aortic valve to the ankle, and by T = tb + tba. The blood pressure is measured at the brachial artery.

Ps = systolic blood pressure, Pd = diastolic blood pressure, PWV = pulse wave velocity, ΔP = Ps – Pd, ρ= blood density, L = the length from the aortic valve to the ankle, T = time taken for the pulse wave to propagate from the aortic valve to the ankle, tb= time between aortic valve's closing sound and the notch of the brachial pulse wave, tba= time between the rise of the brachial pulse wave and rise of the ankle pulse wave, t'b= time between aortic valve's opening sound and rise of the brachial pulse wave. (Modified from Shirai et al. 2006.)

resistance, was administered CAVI was found to decrease. These results suggest that CAVI is independent of blood pressure during measurement but is affected by changes in the contractility of vascular smooth muscle cells. (Shirai et al. 2011b.) CAVI is reported to be independent of changes in blood pressure during measurement also in diabetic subjects (Ibata et al. 2008). Since CAVI is not influenced by blood pressure at the time of the measurement it allows the evaluation of the effect of antihypertensive drugs on arterial stiffness as well as the effect of blood pressure on the properties of the arterial wall (Shirai et al. 2011a).

A positive correlation between CAVI and age has been reported quite extensively in both genders and in different populations (Kubozono et al. 2007; Nakamura et al. 2008; Namekata et al. 2011; Lindholm et al. 2012; Choi et al. 2013; Tanisawa et al. 2015). Thus, CAVI is thought to reflect arterial aging (Choi et al. 2013). CAVI values are on average 0.2 higher in men compared to women at all ages (Shirai et al. 2011a) and men's CAVI seems to be about 5 years ahead of women's at age of 30–60 years and even 10 years ahead of women's CAVI after 60 years of age (Namekata et al. 2011). Increase in CAVI per 10 years of age has been reported to be 0.48 in men and 0.45 in women in a healthy CVD risk-free Korean cohort (Choi et al. 2013) whereas in Japanese subjects CAVI has been found to increase by 0.22–0.66 in both genders per 10 years increase in age (Namekata et al. 2011).

5.2 CAVI and cardiovascular risk

CAVI reflects arteriosclerosis but it is considered to reflect also atherosclerosis (Namekata et al. 2011). Atherosclerotic process in the arterial wall can lead to reduced elasticity and thus increased arterial stiffness (Dobsak et al. 2015) and the use of CAVI as atherosclerotic indicator has been suggested by Horinaka et al. (2011). In general, CAVI shows high values in arteriosclerotic diseases as well as in people with various coronary risk factors, and the improvement of those risk factors is usually associated with decreases in CAVI (Saiki et al. 2016).

CAVI seems to be a good marker of the progression of arteriosclerosis and changes in CAVI can also predict future cardiovascular events (Saiki et al. 2016). CAVI reflects the degree of arteriosclerosis in large-, medium-, and small-sized arteries (Namekata et al. 2011). CAVI is associated with intima-media thickness and arterial plaque (Ibata et al. 2008; Kim et al. 2011) and it might also be useful in indicating the severity of coronary atherosclerosis (Nakamura et al. 2008). Abnormally high CAVI is significantly associated with coronary heart disease (Namekata et al. 2012). CAVI has also been suggested to reflect the severity of cerebral arteriolosclerosis (Sun 2013). A high CAVI has been shown to be an independent predictor of cardiovascular disease with CVD risk being about 2-fold higher with CAVI ≥10 than with CAVI <9 (Kubota et al. 2011).

Additionally, increase in CAVI is associated with smoking (Choi et al. 2013), male gender (Namekata et al. 2011), and drinking more than 3–4 times per week (Namekata et al. 2012). The relationship between CAVI and BMI seems to be U-shaped indicating that individuals with both high and low BMI are at risk of having abnormally high CAVI (Namekata et al. 2012). Increased CAVI is associated also with diabetic nephropathy and neuropathy in type 2 diabetic individuals (Kim et al. 2011). Increased CAVI is found also in individuals with dyslipidemia (Dobsak et al. 2015), diabetes (Namekata et al. 2012), ischemic cerebrovascular diseases (Suzuki et al. 2013), hypertension, and hyperglycemia (Namekata et al. 2011). On the other hand, CAVI is inversely associated with HDL-cholesterol indicating that having high HDL-cholesterol prevents the progression of arteriosclerosis (Namekata et al. 2012; Wang et al. 2013). The difference in CAVI between CVD risk-free individuals and those with increased CVD risk seems to become significant after the age of 40 years (Namekata et al. 2011).

CAVI appears to be associated with glycemic control (Ibata et al. 2008; Horinaka et al. 2011; Nagayama et al. 2013; Homma et al. 2015) and improvement of glycemic control results in decrease in CAVI (Ibata et al. 2013). However, short-term glycemic change does not seem to have influence on CAVI suggesting that that glucose concentration itself does not directly affect CAVI but the effect of glycemic control is indirect through changes in

vascular endothelial or autonomic function (Ibata et al. 2013). Also postprandial hyperglycemia was found to be an independent predictor of increased CAVI in nondiabetic subjects (Tsuboi et al. 2015).

CAVI has been found to be associated with visceral fat area (Nagayama et al. 2013; Tsuboi et al. 2015). Iguchi et al. (2013) reported higher CAVI in overweight and obese subjects with metabolic syndrome compared to those without metabolic syndrome. CAVI can be reduced significantly through weight reduction therapy (Iguchi et al. 2013; Nagayama et al. 2013) and the change in CAVI seems to be associated with change in visceral fat area (Nagayama et al. 2013).

5.3 CAVI and physical activity

Tanisawa et al. (2015) found that CAVI is negatively correlated with VO_{2peak} in middle-aged and elderly Japanese men with and without hypertension independent of age and visceral fat area. However, in normotensive subjects the correlation between VO_{2peak} and CAVI was lost after adjusting for age. Hypertensive individuals with high cardiorespiratory fitness were found to have significantly lower CAVI compared to hypertensive individuals with low cardiorespiratory fitness. However, the blood pressure values did not differ between the groups suggesting that a lower CAVI is not associated with decreased blood pressure in hypertensive individuals with high aerobic fitness. The lower CAVI may result from attenuating effect of high cardiorespiratory fitness on arterial remodeling leading to reduced hypertension-related arterial stiffness. It also appears that the effect of aging on CAVI remains even in individuals with high fitness level and thus, the age-related increase in CAVI cannot be completely eliminated by maintaining a high aerobic fitness level. (Tanisawa et al. 2015.)

The number of exercise sessions per week has been shown to be a significant predictor of CAVI in Finnish firefighters since less than three regular exercise sessions per week was

associated with higher CAVI (Lindholm et al. 2012). Also VO_{2peak} has been identified as a significant predictor of CAVI (Tanisawa et al. 2015). The link between arterial stiffness and cardiorespiratory fitness is further supported by the finding that an increase in CAVI has been shown to correlate with an accelerated decrease in VO_{2max} (Lindholm et al. 2012).

Endes et al. (2016) found self-reported physical activity to be inversely associated with CAVI in ageing population, and this was especially true with vigorous physical activity. In contrast, Kawano et al. (2012) did not find any difference in CAVI, endothelin-1 or NO between elderly rowers and sedentary controls. Low-intensity exercise was reported to acutely decrease CAVI healthy young men but arterial stiffness was improved for longer duration if the low-intensity exercise was divided into two bouts with 20 minutes rest period between the bouts (Wang et al. 2014). The duration of the rest interval seems to be important because the superior effect of moderate-intensity interval exercise was found only with 20 minutes but not with 60 minutes rest period (Zheng et al. 2015). However, when the moderate-intensity exercise of 30 minutes was divided into three 10 minutes bouts the superior effect of interval exercise on CAVI compared to continuous exercise was found with rest intervals of both 10 minutes and 60 minutes (Zhou et al. 2015).

When it comes to resistance training, upper and lower body training seems to have different effects on CAVI. Immediately after lower body resistance training CAVI was reported to be decreased and significantly lower than immediately after upper body resistance training. (Li et al. 2015.) CAVI seems to be also related to muscle mass since higher CAVI was found to be associated with low skeletal muscle mass index in older adults (Sampaio et al. 2014).

6 TYPE 1 DIABETES

Type 1 diabetes, previously known as insulin dependent diabetes, is a chronic disease that is characterized by hyperglycemia resulting from inadequate insulin production by the pancreas. The inadequate insulin production results from destruction of insulin-producing β cells in the islets of Langerhans by self-reactive T lymphocytes which are activated by autoantigen. Insufficient insulin production leads to the typical symptom triad of weight loss, polyuria, and polydipsia, and the risk of ketoacidosis. (Thrower & Bingley 2010.) According to American diabetes Association (2015) type 1 diabetes is defined as the presence of one or more autoimmune markers, including islet cell autoantibodies, autoantibodies to insulin, autoantibodies to GAD (GAD65), autoantibodies to the tyrosine phosphatases IA-2 and IA-2b, and autoantibodies to zinc transporter 8. Type 1 diabetes is a complex disease that develops as the result of multiple genetic and environmental etiological factors. Type 1 diabetes accounts for 5–10% of all cases of diabetes worldwide. (Thrower & Bingley 2010.)

Most individuals with type 1 diabetes have an immune disorder, or even auto-immune mediated disorder. That is, patients commonly demonstrate features of immunological contribution to pathogenesis, such as autoantibodies or genetic associations with genes controlling immune responses. (Atkinson et al. 2014.) There are also some forms of type 1 diabetes with no known etiologies which are called idiopathic diabetes. (American Diabetes Association 2015.)

Recent studies suggest that a series of functional defects in the bone marrow and thymus, immune system, and β cells together lead to loss of insulin production and contribute to the pathogenic process underlying type 1 diabetes. Type 1 diabetes comprises a selective loss of pancreatic β cells. Multiple mechanisms seem to be involved in the loss of β cells in the pathogenesis of type 1 diabetes. The leading feature that distinguishes between type 1 and type 2 diabetes is the presence of autoantibodies against β-cell autoantigens. These

autoantibodies can be present months to years before the onset of clinical symptoms. In type 1 diabetes exogenous insulin replacement is required. (Atkinson et al. 2014.)

The goal of the management of type 1 diabetes is to minimize the hyperglycemic state with medication and therapy. Glycemic control is monitored by measuring glycosylated hemoglobin (HbA1c) that gives an estimate of glycemic status over the past 1–2 months. (Wheatley et al. 2011.) American Diabetes Association (2016) recommends that a reasonable HbA1c goal would be 7 % for nonpregnant adults.

Diabetes impacts almost every vascular bed. The abnormal metabolic state that occurs with diabetes causes changes in the state of arterial structure and function. (American Diabetes Association 2003.) Typically, the diabetic complications are divided into microvascular and macrovascular. Microvascular complications affect the smaller blood vessels, located in the retina of the eyes (retinopathy), the kidney (nephropathy), and the nerves (neuropathy). Macrovascular complications involve the large blood vessels, in the brain, the heart, and the limbs. Hyperglycemia associated with diabetes is thought to be a key factor in the pathogenesis of the complications in type 1 diabetes. (Gordin & Groop 2012.)

6.1 Peripheral arterial disease in diabetes

In individuals with diabetes the risk of atherosclerotic diseases is considerably elevated. This increased risk is independent of other cardiovascular risk factors and additional to them. Individuals with diabetes have a greater risk of developing peripheral arterial disease (PAD) compared to individuals without diabetes. PAD is also more severe and more rapidly progressing in diabetic individuals. It is more common that diabetic individuals develop symptomatic PAD. The prevalence of PAD in diabetic individuals may be as high as 29%, when PAD is defined as an ABI <0.90. (Marso & Hiatt 2006.)

The assessment and management of PAD in diabetic individuals poses some special issues. PAD is associated with higher cardiovascular event rates in diabetic than non-diabetic individuals. In diabetic individuals PAD is also a major risk factor for lower-extremity amputation. (American Diabetes Association 2003.) In fact, there is a need for major amputation five to ten times more often in individuals with than without diabetes. In diabetic individuals also the prevalence of intermittent claudication is twice as high as in non-diabetic individuals. (Norgren et al. 2007.)

Diabetes, together with smoking, is the strongest risk factor for PAD. An important difference between these two risk factors is that diabetes is most strongly associated with PAD on the vessels below the knee while other risk factors like smoking and hypertension are associated with PAD on more proximal vessels. The risk of PAD increases with age, duration of diabetes, and presence of peripheral neuropathy in diabetic individuals. The presence of peripheral neuropathy affecting the pain perception, the lack of uniform screening modalities, and the degree of asymptomatic disease in diabetic individuals have hindered determining the true prevalence of PAD in individuals with diabetes. (American Diabetes Association 2003.)

6.1.1 Pathophysiology of PAD in diabetes

The biology of PAD in diabetes is not fully known but it is likely that the atherogenic changes seen with other forms of atherosclerotic disease are generally similar also in patients with diabetes and PAD (American Diabetes Association 2003). The pathophysiology of PAD is thought to be alike in both the diabetic population and the non-diabetic population (Marso & Hiatt 2006). Diabetes is associated with proatherogenic changes, such as increases in vascular inflammation, alterations in blood cells and hemostatic factors, and derangements in the cellular components of the vasculature, which increase the risk for accelerated atherogenesis and poor outcomes. Abnormally elevated

CRP levels are seen in individuals with impaired glucose regulation syndromes, like diabetes. (American Diabetes Association 2003.)

In individuals with type 1 diabetes the endothelium is constantly subject to many stressors promoting the development of endothelial dysfunction (DiMeglio et al. 2010). These stressors include a low-grade inflammation in which both cytokine- and COX-mediated inflammatory pathways seem to be involved. The increased basal level of important inflammatory compounds $PGF_{2\alpha}$ and IL-6 in type 1 diabetic individuals is thought to be associated with hyperglycemia. (Basu et al. 2005.)

Another factor contributing to the endothelial dysfunction is oxidative stress. It is well documented that the level of lipid peroxidation products in the plasma of human diabetics is increased. Studies have also found increased oxidative stress associated with diabetes in erythrocytes, liver, brain, heart, retina, lense, kidney and nerve cells. This elevated oxidative stress can lead to oxidative modification of plasma lipoproteins which has been associated with an increased risk of cardiovascular disease and atherosclerosis. There are at least two possible mechanisms that could explain the association between diabetes and oxidative stress (figure 11). On the one hand hyperglycemia may lead to increased production of oxygen radicals through glycation of proteins. Also auto-oxidation of glucose or ketoaldehydes as well as increased activity of the cytochrome P450 system may be involved in generating oxygen radicals in the state of hyperclycemia. (Jain et al. 2006.) In diabetic individuals the glucose uptake of platelets is not downregulated despite of hyperglycemia contributing to increased oxidative stress and leading to platelet aggregation (American Diabetes Association 2003).

On the other hand, increased oxygen radicals and oxidative stress may result from ketosis. In addition to hyperglycemia, ketosis in frequently seen in individuals with type 1 diabetes and it is known to be another risk factor for oxidative stress. (Jain et al. 2006.) Diabetic ketoacidosis forms in a state of insulin deficiency when alternative energy sources other

than glucose are needed for energy production. This leads to increased lipase activity and free fatty acid release from adipose tissue. Part of these fatty acids is broken down into ketones (acetone, acetoacetate, and β-hydroxybutyrate) that accumulate rapidly in the body. (Westerberg 2013.) The exact mechanisms by which ketones produce excess oxygen radicals and contribute to the development of vascular disease are unclear. However, ketosis has been linked to elevated cellular oxidative stress in diabetic population and it appears that frequent episodes of ketosis may lead to increased oxidative stress. This way it seems plausible that the increase in oxidative stress resulting from hyperglycemia or ketosis play a role in the vascular inflammation and vascular disease associated with type 1 diabetes. (Jain et al. 2006.)

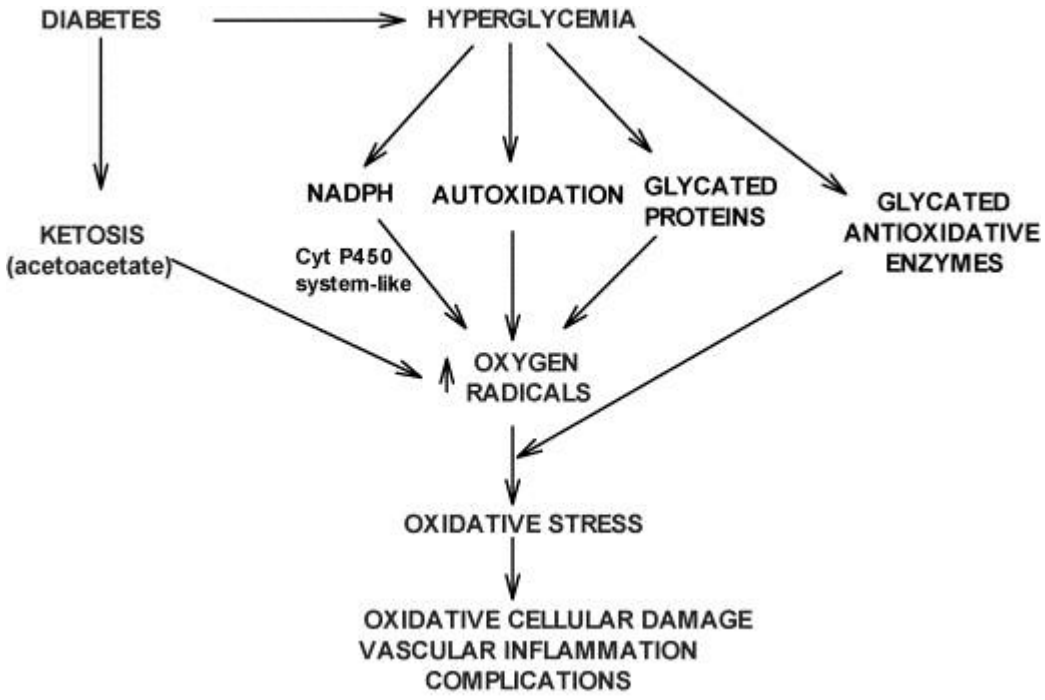

FIGURE 11. Possible mechanisms of excess oxidative cellular damage in type 1 diabetes. (Jain et al. 2006.)

Generalized endothelial cell dysfunction is common in individuals with PAD and diabetes. Endothelial cell dysfunction affects to increase arterial susceptibility to atherosclerosis.

Nitric oxide (NO), which is a strong vasodilator acting to inhibit platelet activation and vascular smooth muscle cell migration, is synthesized by endothelial cells in healthy blood vessels. However, in diabetes NO concentrations are reduced. Furthermore, diabetes is associated with increased production of vasoconstrictors, stimulation of atherogenic pathways in vascular smooth muscle cells, enhanced platelet aggregation, and increased blood coagulability. These alterations in metabolism contribute to the increased thrombotic potential representative of diabetes. (Marso & Hiatt 2006.)

In diabetes there are many mediators of endothelial cell dysfunction derangement of nitric oxide (NO) bioavailability being an important collective path. NO, in addition to having a potent vasodilating effect, also acts to limit inflammation by modulating leukocyte-vascular wall interactions. Additionally, NO prevents vascular smooth muscle cell migration and proliferation and constrains platelet activation. (American Diabetes Association 2003.) The reduced synthesis or secretion of NO also causes increased thickening of the vessel wall (Izar et al. 2012). As a result, the disturbance of normal NO homeostasis can lead to atherosclerosis through cascade of events in the vasculature (American Diabetes Association 2003).

The effects of endothelial cell dysfunction are involved in increasing the local inflammatory state of the vascular wall. The impairment of normal NO function and local increases in proinflammatory factors are associated with increased leukocyte chemotaxis, adhesion, transmigration, and transformation into foam cells the latter being the earliest precursor of atheroma formation. Diabetes is also linked to considerable abnormalities in vascular smooth muscle cell function stimulating proatherogenic activity in these cells. These effects are thought to promote the formation of atherosclerotic lesions. Individuals with diabetes may also have elevated blood viscosity and fibrinogen the latter being associated with the development, presence, and complications of PAD. (American Diabetes Association 2003.)

NO homeostasis is affected by hyperglycemia, insulin resistance, and free fatty acid production. Hyperglycemia inhibits the functioning of endothelial cell nitric oxide synthase and increases the production of reactive oxygen species, which leads to impairment in the vasodilator homeostasis. Insulin resistance is associated with excess liberation of free fatty acid which for example inhibits an endothelial nitric oxide synthase (eNOS) agonist pathway and increases the production of reactive oxygen species leading to impairment of NO homeostasis. (American Diabetes Association 2003.)

6.1.2 Endothelial dysfunction and arterial stiffness

The findings of Brooks et al. (1999) suggest that the effects of type 1 diabetes on central arterial pressure, cardiac workload, and coronary perfusion are analogous to that of aging. Compared to age-matched controls increased augmentation index seems to be significantly associated with type I diabetes in relatively young subjects, but only in men. In addition, type I diabetes has been found to be an independent predictor of augmentation index. (Brooks et al. 1999.) Diabetes, hypertension as well as aging itself also amplify the vascular changes that result in arterial stiffening. Therefore it seems no surprise that stiffening of the arteries is consistently observed in individuals with diabetes across all age groups. (Zieman et al. 2005.)

It has been suggested that the toxic effect of glucose may be one factor leading to stiffening of arteries and subsequent vascular complications in diabetes. The pathway through which high blood glucose produces functional and structural changes in the arteries is complex, involving at least various metabolic, hemodynamic, and intracellular factors together with growth factors and inflammatory components. This ultimately leads to disturbed function of the inner layer of the arteries, the endothelium. (Gordin & Groop 2012.)

The loss of NO-mediated endothelium-dependent vasodilatation characterizes endothelial dysfunction. Endothelial dysfunction is thought to be strongly associated with arterial

stiffness. Arterial stiffness seems to be elevated in type 1 diabetics even before the presence of clinically detectable diabetic complications. Micro- and macrovascular complications further increase arterial stiffness. It has also been shown that individuals with type 1 diabetes suffer from premature arterial aging indicated by increased pulse pressure. Endothelial dysfunction is already present in individuals with type 1 diabetes and microalbuminuria. Arterial stiffness in diabetics is correlated with the duration of diabetes and the exposure to hyperglycemia. Therefore it seems likely that chronic hyperglycemia and other chronic metabolic changes associated with diabetes lead to the stiffening of the arteries. (Gordin & Groop 2012.)

Giannattasio et al. (1999) have shown that in young men (about 35 years of age) with type I diabetes and no macrovascular complications radial artery, carotid artery and aortic distensibility are reduced compared to age-matched controls, whereas carotid and radial artery wall thickness are increased. With the exception of carotid artery distensibility, these changes were visible also in subjects without clinical evidence of microvascular complications, although the magnitude of the changes increased with the duration of disease and was more pronounced in those with microvascular complications. These alterations in arterial distensibility and wall thickness observed not only in diabetic hypertensive subjects but also in normotensive individuals. An inverse relationship was found between carotid artery and aortic distensibility and patient's age, duration of diabetes and blood pressure in diabetic subjects. The researchers concluded that type I diabetes is characterized by diffuse alterations in arterial function and structure that progress with increasing severity of diabetes. It is important to note that in most arteries these alterations can be seen already when there is no evidence of diabetes-related complications or blood pressure abnormalities. These results suggest that generalized vascular abnormalities are a very early subclinical phenomenon in type I diabetes. (Giannattasio et al. 1999.)

6.2 Limitations of ABI in diabetics

The estimated prevalence of PAD in diabetic individuals is high. Therefore it is recommended by American Diabetes Association that ABI screening should be performed in people with diabetes over 50 years of age. In the case of a normal ABI value, the test should be repeated every 5 years. Also in individuals <50 years of age with diabetes and other PAD risk factors (e.g. smoking, hypertension, hyperlipidemia, or duration of diabetes >10 years) it is recommended that a screening ABI should be considered. (American Diabetes Association 2003.)

However, the use of ABI in the diagnosis of PAD in diabetic population may have some difficulties. In fact diabetes mellitus has been validated as one of the risk factors for inaccurate ABI in diagnosis of PAD (Nam et al. 2010). The medial artery calcification (MAC) which is highly prevalent in diabetic subjects has an effect on the interpretation of ABI. MAC causes arterial wall stiffness leading to poorly compressible vessels. This results in high ankle pressures, and thus a high ABI. Therefore the sensitivity of ABI may be limited in case of complicated or longstanding diabetes and normal ABI values may not always be enough to rule out the diagnosis of PAD. (Potier et al. 2011.)

High ABI values may also lead to underestimation of the prevalence of PAD in diabetes. It is possible that ABI values between 0.9 and 1.3 would be falsely considered as normal and higher values could not be interpreted. (Potier et al. 2011.) The elevated ABI values may also result from collateral circulation, which maintains blood flow to the lower limb in spite of the obstruction (Xu et al. 2010). Therefore it should be noted that also high ABI values in diabetes could be indicative of PAD (Potier et al. 2011).

Also the presence of bilateral subclavian-axillary artery occlusive disease affects ABI. This would lead to artificially low brachial pressures in both arms and thus artificially elevated ABI. The trend over time, rather than the absolute value, is therefore recommended as the

clinically most important for an individual. (Caruana et al. 2005.) Either the measurement itself may not always succeed in people with diabetes. Because of non-compressible vessels, in some diabetic individuals blood pressure at the ankle cannot be recorded and therefore additional non-invasive testing is needed to confirm the diagnosis. Such tests may include toe systolic pressures, pulse volume recordings, transcutaneous oxygen measurements or vascular imaging (i.e. with duplex ultrasound). (Norgren et al. 2007.)

Thus, ABI can be used in diabetic individuals but the values should be interpreted carefully and according to the clinical situation. It should be kept in mind that normal values are not sufficient to rule out the diagnosis of PAD. (Potier et al. 2011.) Therefore, in unclear and clinically suspicious situations other supplementary examinations in addition to ABI may be necessary (Norgren et al. 2007; Nam et al. 2010; Potier et al. 2011).

7 RESEARCH QUESTIONS AND HYPOTHESIS

Question 1. Is there a difference in ABI or CAVI between young men with or without type 1 diabetes?

Hypothesis 1: There are no previous studies investigating ABI in young type 1 diabetic only. In a mixed group of type 1 and type 2 diabetic subjects ABI has not been found to be different compared to nondiabetic controls (Ibata et al. 2013). The participants of this study are relatively young and arterial obstruction may not have developed yet. Thus no difference in ABI is expected between young men with and without type 1 diabetes. CAVI is hypothesized to be different between type 1 diabetic and nondiabetic participants since CAVI has been found to be higher in individuals with type 1 diabetes than in nondiabetic subjects (Ibata et al. 2008; Ibata et al. 2013; Iwasa et al. 2016; Namekata et al. 2016).

Question 2. Are the measured ABI and CAVI values associated with cardiorespiratory fitness or leisure time physical activity?

Hypothesis 2: ABI is not expected to be associated with cardiorespiratory fitness and leisure-time physical activity. ABI represents arterial obstruction (MacDougall et al. 2008) and if no obstruction has developed, as hypothesized, no effect of exercise on ABI is expected. CAVI is hypothesized to be associated with cardiorespiratory fitness and leisure-time physical activity, at least in subjects with type 1 diabetes. VO_{2peak} has been found to be negatively related to CAVI (Tanisawa et al. 2015) and physical activity to be inversely associated with CAVI (Endes et al. 2016).

8 METHODS

8.1 Subjects

Twenty-nine male volunteers participated in the study. Twelve of the participants were individuals with type 1 diabetes and seventeen were healthy controls. Exclusion criteria were age of <18 or >45 years, previous diagnosis or previous clinical evidence of microvascular complications (i.e., retinopathy, nephropathy neuropathy), hypertension, or any chronic disease other than diabetes for the subjects in the T1D group. Exclusion criteria included also β-blocker medication, medication influencing glucose homeostasis except for multiple daily insulin injections for diabetic subjects, physical disability, substance abuse, smoking, and elite athlete status. A written informed consent to participate in the study was obtained from all subjects. The study was approved by the Ethics Committee of Hospital District of Helsinki and Uusimaa, and conforms to the declaration of Helsinki.

8.2 Study protocol

This study was a cross-sectional subanalysis of an "Exercise, Diet and Genes in T1D" (EDGE) Helsinki project. All measurements were performed in the Department of Sports and Exercise Medicine (University of Helsinki) and the Clinic for Sports and Exercise Medicine (Foundation for Sports and Exercise Medicine). The experiments were performed between years 2009 and 2012.

The subjects were instructed to abstain from alcohol for at least 24 h and physical exercise for at least 12 h before every visit. The first visit consisted of pre-exercise measurements, ABI and CAVI measurements, and cardiorespiratory exercise test. Participants reported to the laboratory 2–3 hours after a meal. All subjects completed a preliminary questionnaire concerning personal health, medical history, smoking habits, and physical activity, and their

height and weight were measured. All participants went through pre-exercise measurement at rest that included a 12-lead electrocardiography (ECG), a flow-volume spirometry test (Medikro Spiro 2000, Medikro Oy, Kuopio, Finland), and examination by a physician to ensure suitability for exercise testing. ABI and CAVI were also measured before exercise testing. Before and after the exercise test blood glucose concentration was analyzed from a fingertip capillary blood sample (Glucocard x-meter, Arkray Factory, Inc., Shiga, Japan) to ensure that blood glucose was within the acceptable range (Colberg et al. 2016). None of the subjects was hypoglycemic after the exercise test.

All subject performed a cardiopulmonary exercise test on a cycle ergometer (Monark Ergomedic 839E, Monark Exercise AB, Vansbro, Sweden). Before the step incremental protocol the subjects sat relaxed on a cycle ergometer for 5 minutes at rest which was followed by 5 min baseline unloaded cycling. After this the step incremental exercise protocol (40 W per 3 min) was initiated with a work rate of 40 W. Rating of perceived exertion (RPE) was asked at the end of each work load. The subjects continued exercising until volitional fatigue. The test was monitored by an experienced physician. On a separate visit glycosylated hemoglobin (HbA1c) was measured only in subjects with type 1 diabetes from blood drawn from antecubital vein after overnight fast.

8.3 Data collection

During the incremental exercise test breath-by-breath ventilation was measured by a low-resistance turbine (Triple V, Jaeger Mijnhardt, Bunnik, The Netherlands) and with a respiratory mass spectrometry (AMIS 2000, Innovision A/S, Odense, Denmark). Maximal oxygen uptake (VO_{2max}) was determined as the highest 60-s average value (l/min). The absolute VO_{2max} (l/min) was normalized for body mass to yield relative VO_{2max} (ml/kg/min). Heart rate and electrical activity of the heart were monitored by a 2-lead ECG (PowerLab, ADInstruments Ltd, Oxford, United Kingdom) throughout the exercise test. Leisure-time physical activity was obtained from the preliminary questionnaire. To assess leisure-time

physical activity, the following question was asked: “If you think about your past three months and physical activity sessions lasting more than 20 minutes in all settings (e.g., commuting, walking a dog, recreation, sport), how many times a week and how long at a time have you engages in physical activity?”.

ABI, CAVI, and blood pressure at rest were measured using VaSera VS-1500 (Fukuda Denshi Co. Ltd., Tokyo, Japan). All subjects rested in supine position for 10 minutes before the measurement. The cuffs were placed around both arms and ankles of the subject and the measurements were then performed automatically. Mean arterial pressure (MAP) was calculated as MAP = (2/3)DBP + (1/3)SBP and pulse pressure as PP = SBP – DBP. The reproducibility of CAVI has been reported range from 2.8 % to 3.8 % which is considered to be within satisfactory range since 5 % is generally thought to be the limit for clinical laboratory testing (Shirai et al 2006; Kumagai et al. 2009). The sensitivity and specificity for CAVI cut-off level of 8.8 to detect coronary atherosclerosis has been reported to be 82 % and 76 %, respectively (Nakamura et al. 2008). For detection of a mean carotid IMT >0.90 mm CAVI 8.95 have shown sensitivity and specificity of 70 % and 64 %, respectively (Gomez-Sanchez et al. 2015). The specificity of ABI ≤0.90 to diagnose PAD seems to vary between 83.3 % and 99.0 %, and sensitivity range from 15.0% to 79.0% (Xu et al. 2010).

8.4 Statistical analysis

The normality of the data was determined using Saphiro-Wilk -test. All parameters are presented as mean ± standard deviation. To test the statistical significance of group differences independent samples t-test was used. Relationships between key variables were determined by the Pearson correlation coefficient. In the case where a variable was not normally distributed non-parametric tests (Mann-Whitney U-test for group comparisons and Spearman correlation) were used. Two-tailed $p<0.05$ was considered to mark statistical

significance. Statistical analysis was completed using IBM SPSS Statistics Version 24 software (SPSS Inc., Chicago, IL, USA).

9 RESULTS

The descriptive characteristics of the study sample, control group, and type 1 diabetes group (T1D) are summarized in table 1 together with the mean duration of diabetes and HbA1c of the T1D group. There were no statistical differences in the age, height, weight, or BMI between control and T1D group. Mean duration of diabetes in T1D group was 13 ± 7 years and mean HbA1c was 7.5 ± 0.7 %.

TABLE 1. The descriptive characteristics of the study sample, control group, and T1D group.

	Study sample	Control	T1D
n	29	17	12
Age (y)	32.8 (± 6.5)	32.9 (± 6.4)	32.7 (± 6.9)
Height (cm)	180.9 (± 5.6)	181.2 (± 5.2)	180.5 (± 6.5)
Body mass (kg)	82.2 (± 10.0)	83.1 (± 9.8)	80.9 (± 10.6)
BMI	25.1 (± 2.8)	25.3 (± 2.8)	24.8 (± 2.9)
Duration of T1D (y)			13 (± 7)
HbA1c (%)			7.5 (± 0.7)

SD = standard deviation, BMI = body mass index, T1D = type 1 diabetes group, HbA1c = glycosylated hemoglobin

The absolute and relative maximal oxygen uptake (VO_{2max}), ABI, CAVI, blood pressure variables, calculated artery age and leisure time physical activity in the whole study sample, in the control group, and in the type 1 diabetes group are presented in table 2. There was a significant difference in both relative (42.7±7.5 ml/kg/min vs. 35.9±4.8 ml/kg/min, p=0.01) and absolute (3.5±0.5 l/min vs. 2.9±0.6 l/min, p=0.004) VO_{2max} between the control and the T1D groups, respectively (table 3). A significant difference between the control group and the T1D group was also found in right (6.5±0.6 vs. 7.1±0.5, p=0.006) and left (6.4±0.6 vs. 7.1±0.4, p=0.004) CAVI but not in ABI (table 3). There were no statistically significant

differences in blood pressure measures or leisure-time physical activity between the control and the T1D groups.

TABLE 2. Maximal oxygen uptake, ABI, CAVI, blood pressure, and leisure time physical activity in the study sample, control group and T1D.

	Study sample	Control	T1D
VO_{2max} (l/min)	3.3 (± 0.6)	3.5 (± 0.5)	2.9 (± 0.6)
VO_{2max} (ml/kg/min)	39.9 (±7.2)	42.7 (± 7.5)	35.9 (± 4.8)
ABI right	1.1 (± 0.1)	1.1 (± 0.1)	1.1 (± 0.1)
ABI left	1.1 (± 0.1)	1.1 (± 0.05)	1.1 (± 0.1)
CAVI right	6.7 (± 0.6)	6.5 (± 0.6)	7.1 (± 0.5)
CAVI left	6.7 (± 0.6)	6.4 (± 0.6)	7.1 (± 0.4)
SBP (mmHg)	127.7 (± 10.6)	128.3 (± 10.6)	126.8 (± 11.0)
DBP (mmHg)	77.1 (± 7.2)	77.6 (± 6.1)	76.3 (± 8.8)
MAP (mmHg)	94.0 (± 7.8)	94.5 (± 7.1)	93.2 (± 9.0)
PP (mmHg)	50.6 (± 7.4)	50.7 (± 7.4)	50.6 (± 7.7)
LTPA (min/wk)	273 (± 155)	287 (± 159)	253 (± 154)

T1D = type 1 diabetic group, VO_{2max} = maximal oxygen uptake, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, PP = pulse pressure, LTPA = leisure-time physical activity

Leisure-time physical activity had a significant inverse correlation with right ($r=-0.72$, $p<0.01$) and left CAVI ($r=-0.68$, $p<0.05$) (figure 12a and 12b, respectively) in the T1D group but not in the control group (figure 13) or in the study sample. Leisure-time physical activity was not correlated with right or left ABI in any of the groups. Absolute and relative VO_{2max} were not correlated with ABI or CAVI in the control group or the T1D group. In the whole study sample absolute VO_{2max}, but not relative VO_{2max}, correlated with left CAVI ($r=-0.38$, $p<0.05$, figure 14b) but the correlation with right CAVI didn't reach significance ($p=0.053$, figure 14a).

TABLE 3. The differences between control group and T1D group in VO_{2max}, CAVI, ABI, systolic and diastolic blood pressure, mean arterial pressure, pulse pressure, and LTPA.

	$\Delta\bar{x}$	p	95 % CI
VO_{2max} (l/min)	0.6	0.004 *	0.20735, 0.99343
VO_{2max} (ml/kg/min)	6.8	0.010 *	1.772, 11.840
ABI right	0.0	0.696	-0.084, 0.057
ABI left	0.0	0.890	-0.064, 0.073
CAVI right	-0.6	0.006 *	-1.034, -0.193
CAVI left	-0.6	0.004 *	-1.060, -0.219
SBP	1.5	0.721	-6.854, 9.776
DBP	1.4	0.616	-4.253, 7.047
MAP	1.4	0.651	-4.747, 7.472
PP	0.1	0.982	-5.773, 5.900
LTPA	34.3	0.567	-87.061, 155.590

VO_{2max} = maximal oxygen uptake, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, PP = pulse pressure, LTPA = leisure-time physical activity, CI = confidence interval

BMI correlated negatively with right (r=-0.62, p<0.05) and left CAVI (r=-0.67, p<0.05) but only in the T1D group. ABI did not correlate with BMI in any of the groups. Leisure-time physical activity did not correlate with absolute (r=0.21, p=0.510) or relative VO_{2max} (r=-0.03, p=0.933) in the T1D group but in the control group relative VO_{2max} and LTPA correlated positively (r=0.57, p<0.05).

Pulse pressure was correlated with right CAVI (r=-0.85, p<0.001) and left CAVI (r=-0.83, p=0.001) only in the T1D group. Absolute VO_{2max} correlated positively with systolic blood pressure (r=0.72, p<0.01), diastolic blood pressure (r=0.60, p<0.05) and mean arterial pressure (r=0.70, p<0.05) in T1D group and in the whole study sample (r=0.46, p<0.05; r=0.41, p<0.05 and r=0.47, p<0.05, respectively) but not in the control group. No correlation was found between relative VO_{2max} and blood pressure measures in any of the

groups. Leisure-time physical activity did not correlate with systolic blood pressure, diastolic blood pressure, or mean arterial pressure in any of the groups.

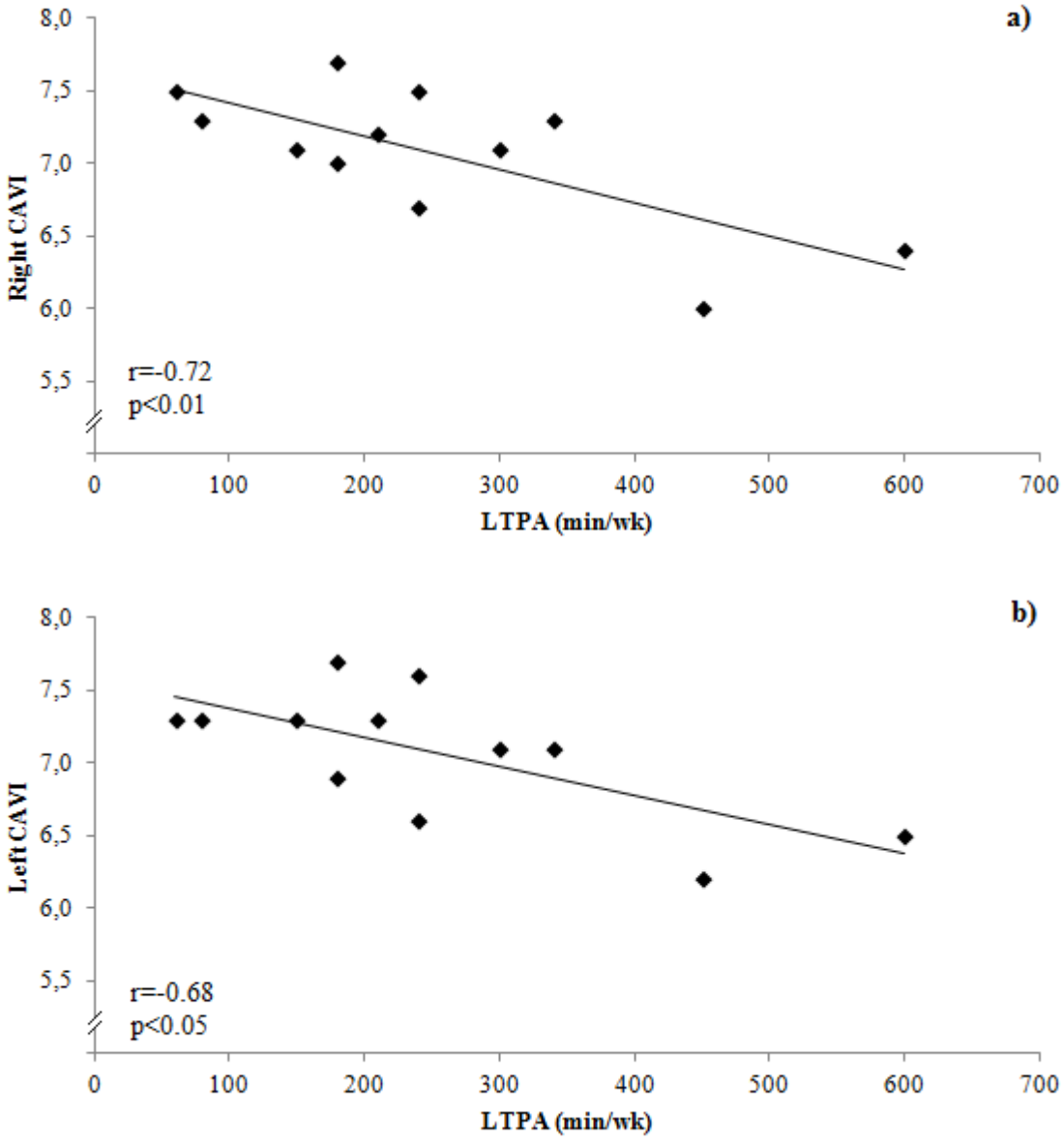

FIGURE 12. The relationship between leisure-time physical activity (LTPA) and CAVI in T1D group.

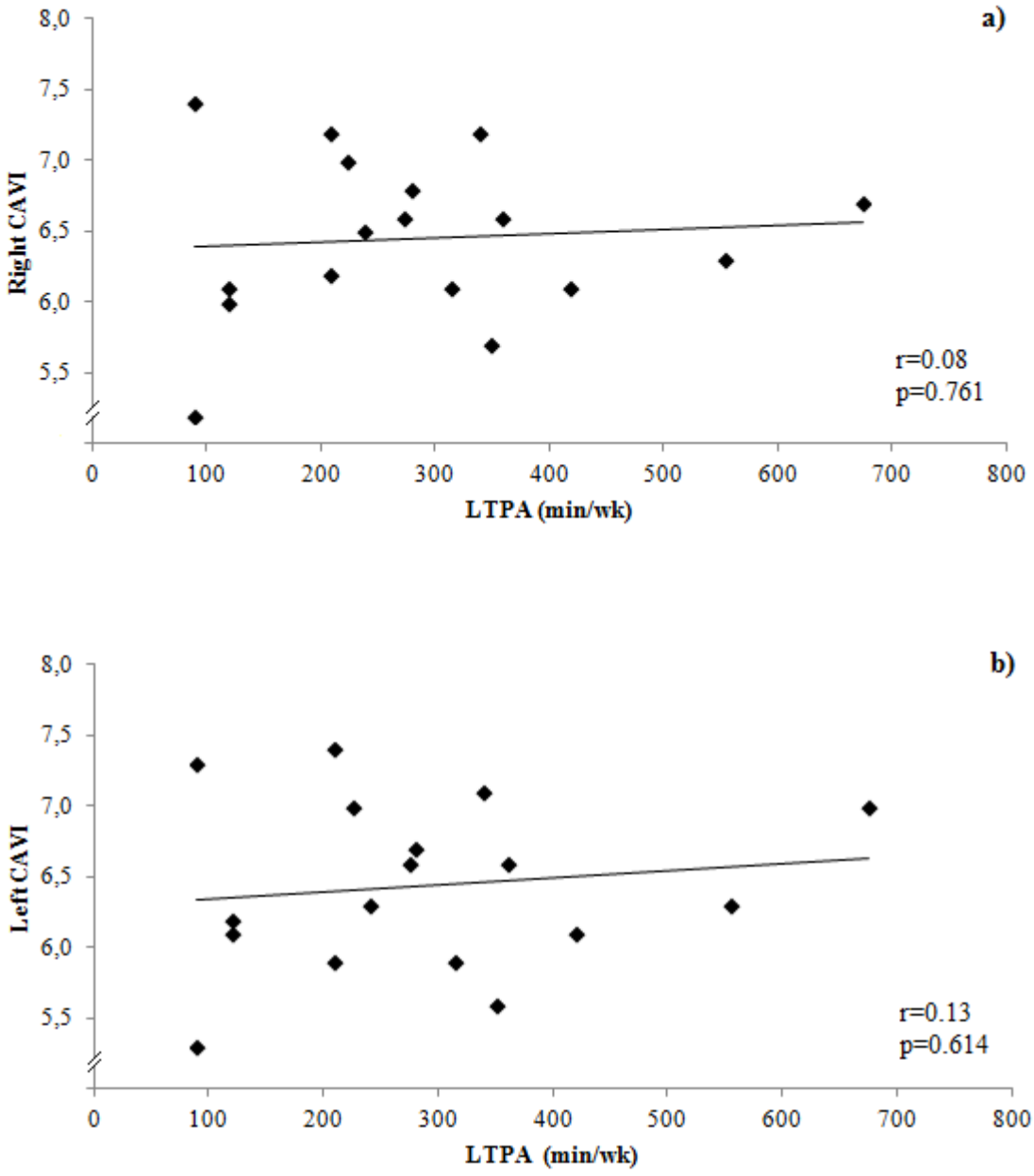

FIGURE 13. The relationship between leisure-time physical activity (LTPA) and CAVI in control group.

There was no correlation between HbA1c and absolute VO_{2max} (r=-0.288, p=0.391) or relative VO_{2max} (r=-0.148, p=0.200) in the T1D group. No correlation between diabetes

duration and absolute VO_{2max} (r=0.411, p=0.184) or relative VO_{2max} (r=0.169, p=0.599) was found either. ABI and CAVI were not correlated with HbA1c or duration of diabetes.

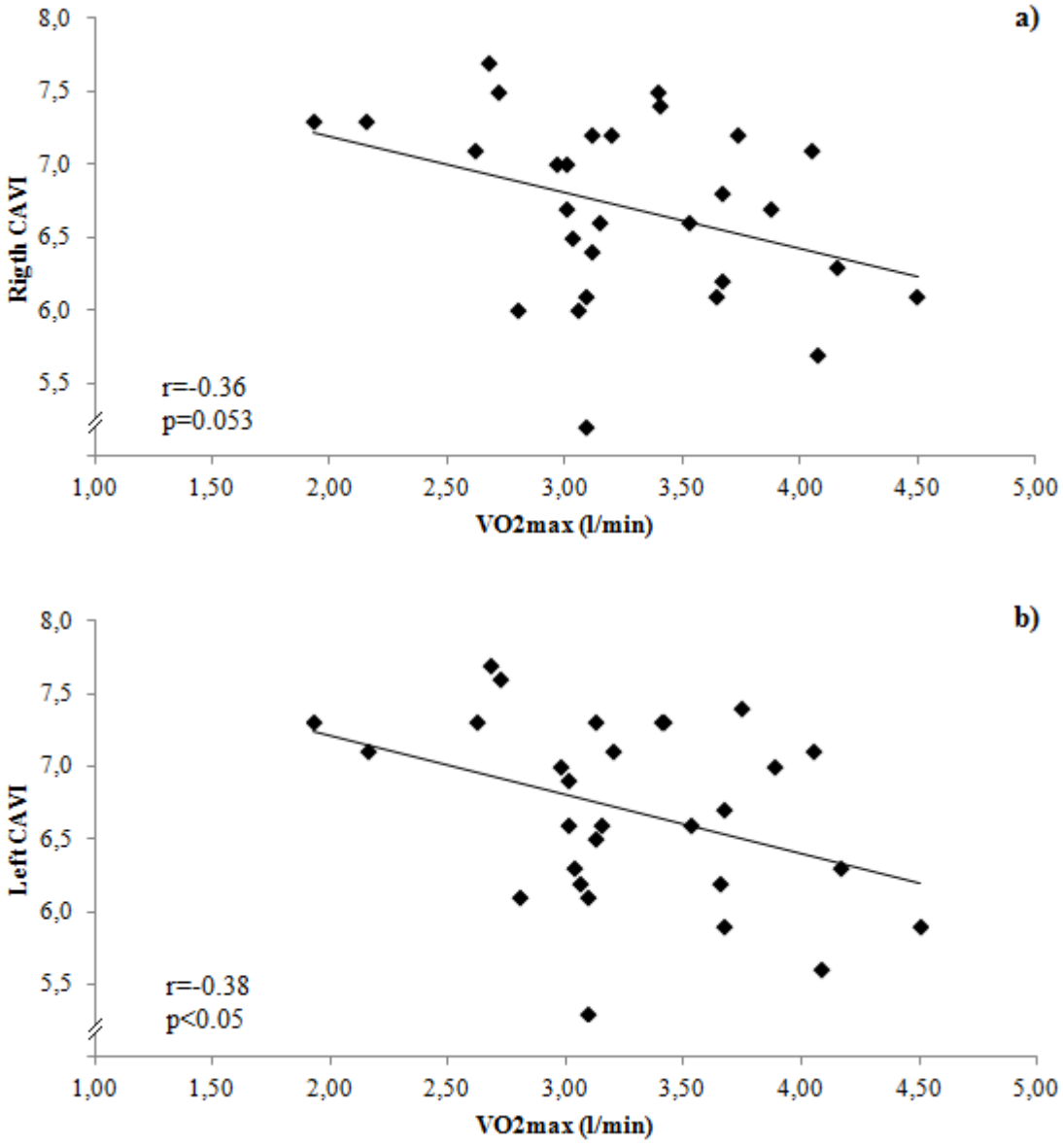

FIGURE 14. The relationship between absolute VO_{2max} and CAVI in the whole study sample.

10 DISCUSSION

Type 1 diabetes and the abnormal metabolic state associated with it affect nearly every vascular bed in the human body (American Diabetes Association 2003). The relative risk of cardiovascular disease can be even 10-fold higher in individuals with type 1 diabetes compared to non-diabetic individuals (Daneman 2006). Since micro- and macrovascular diseases account for majority of the increased morbidity and mortality associated with type 1 diabetes (Daneman 2006), early detection of vascular changes would be important in order that a proper treatment plan can be made to effectively manage the future risk of cardiovascular events.

In this study it was found that CAVI representing arterial stiffness is increased in young men with type 1 diabetes compared to matched non-diabetic individuals. CAVI was also found to be positively associated with leisure-time physical activity in type 1 diabetic but not in non-diabetic individuals. In addition, cardiorespiratory fitness of type 1 diabetic individuals was found to be lower than in controls despite of similar self-reported leisure-time physical activity.

10.1 CAVI

In this study both right and left CAVI were significantly higher in type 1 diabetic men than in healthy controls. This is in line with previous studies showing higher CAVI in diabetic compared to nondiabetic individuals (Ibata et al. 2008; Ibata et al. 2013; Iwasa et al. 2016; Namekata et al. 2016). As CAVI measures the stiffness of the aorta, femoral artery and tibial artery as a whole (Shirai et al. 2006), this result means that these individuals with type 1 diabetes had increased arterial stiffness compared to healthy controls. Although suggesting stiffer arteries than in healthy controls, the CAVI value of these diabetic subjects (7.1±0.5 for right, 7.1±0.4 for left CAVI) would still have been categorized as normal, when

CAVI ≥9 is considered the diagnostic threshold for cardiovascular disease (Kotani & Remaley 2013).

Reduced aortic and radial artery distensibility (Giannattasio et al. 1999) and decreased distensibility of femoral artery (Kool et al. 1995) have been reported in young uncomplicated type 1 diabetic individuals in comparison with healthy controls suggesting increased arterial stiffness. Also arterial compliance has been found to be reduced (Berry et al. 1999) and systemic arterial stiffness increased (Wilkinson et al. 2000) in young type 1 diabetic subjects. Gordin et al. (2007) found higher stiffness of the resistance arteries in young uncomplicated type 1 diabetic men with HbA1c levels similar to this study compared to healthy controls. These studies support the finding of this study and suggest that the slightly increased yet still normal arterial stiffness may be a very early subclinical indicator of vascular abnormalities in individuals with type 1 diabetes.

It is known that diabetes impacts almost every vascular bed and causes changes in the arterial structure and function (American Diabetes Association 2003). Diabetes is associated with increased production of vasoconstrictors and reduction in NO concentrations which both can contribute to arterial stiffening (Marso & Hiatt 2006). Hyperinsulinemia resulting from subcutaneous insulin injections may be one factor causing vasoconstriction through increased sympathetic nervous activity (Berry et al. 1999). On the other hand, individuals with type 1 diabetes have been reported to be resistant to the ability of insulin to decrease large artery stiffness (Weserbacka et al. 2000). Gordin et al. (2007) proposed that in young type 1 diabetic patients increased vascular tone, resulting from chronic hyperglycemia induced functional alterations, rather than structural changes in the arterial wall would explain the increased arterial stiffness. However, Giannattasio et al. (1999) found also increased radial and carotid artery wall thickness in type 1 diabetic subject without microvascular complications suggesting involvement of altered arterial wall structure in the reduced arterial ditensibility. Hyperglycemia typically present in diabetic individuals also leads to the formation of advanced glycation end-products and the accumulation of AGEs damage endothelial function (Kool et al. 2005). However, no relationship has been found

between arterial compliance and flow mediated dilation suggesting that arterial compliance may not be associated with the endothelial functional capacity in type 1 diabetes (Berry et al. 1999).

One affecting factor may also be the intensity of physical activity. Previous studies have shown lower ventilatory threshold in type 1 diabetic individuals that may favor exercising at lower intensities compared to healthy controls (Komatsu et al. 2010; Peltonen et al. 2012). In addition, Endes et al. (2016) have reported especially vigorous physical activity to be associated with lower arterial stiffness. Thus, control subjects of this study may have had a higher physical activity intensity which could have contributed to lower CAVI.

The toxic effect of glucose has been proposed to be one factor leading to stiffening of the arteries and subsequent vascular complications in diabetes (Gordin & Groop 2012). In this study HbA1c of diabetic participants was slightly elevated suggesting suboptimal glycemic control which may have affected the higher CAVI. Previously acute hyperglycemia has been shown to reduce leg blood flow, which would suggest a vasoconstrictive effect of elevated plasma glucose levels (Giugliano et al. 1997). Acute hyperglycemia has been found to increase arterial stiffness also in type 1 diabetic men (Gordin et al. 2007). It has been hypothesized that hyperglycemia might act through an increase in the production of free radicals which would suppress NO availability (Giugliano et al. 1997).

Contradictory, HbA1c and duration of diabetes were not found to be correlated with CAVI. Previous studies are inconsistent some studies reporting no association between HbA1c and CAVI or arterial stiffness (Kool et al. 1995; Berry et al. 1999; Giannattasio et al. 1999; Wilkinson et al. 2000; Kim et al. 2011; Iguchi et al. 2013) but some studies reporting positive correlation between CAVI and HbA1c (Ibata et al. 2008; Horinaka et al. 2011; Nagayama et al. 2013; Homma et al. 2015). The missing association between CAVI and HbA1c would suggest that glycemic control may not necessarily be associated with the early changes in vascular stiffness in such specific group as young type 1 diabetics. In fact,

Brooks et al. (1999) did not find HbA1c to be a significant determinant of aortic augmentation index in young type 1 diabetic subjects.

In respect of the relationship between diabetes duration and arterial stiffness some studies (Berry et al. 1999) have found no association while some (Giannattasio et al. 1999; Wilkinson et al. 2000) have found a correlation between arterial stiffness and diabetes duration. Since arterial stiffness (Cockcroft et al. 2000; Mattace-Raso et al. 2006) and CAVI (Choi et al. 2013; Endes et al. 2016) increase with age and the duration of diabetes in general increases with aging, a relationship between diabetes duration and arterial stiffness would be likely. Nevertheless, no correlation between age and CAVI was found in this study. The lack of correlations may be explained by the small sample size in this study or the type 1 diabetic group may have been too homogenous in respects of these variables. On the other hand, these results might indicate that in young men with type 1 diabetes and normal CAVI the duration of diabetes and age are not associated with arterial stiffness.

The mean leisure-time physical activity in both control and T1D group met the recommendation of American College of Sports Medicine of ≥150 minutes of exercise per week (Garber et al. 2011). In type 1 diabetic subjects CAVI was found to correlate negatively with leisure-time physical activity. That is, those with greater amount of leisure-time physical activity were more likely to have lower CAVI implying less stiff arteries. However, no association was found between CAVI and VO_{2max}. This could be interpreted to mean that the volume of physical activity rather than the cardiorespiratory fitness itself is related to arterial stiffness in young individuals with type 1 diabetes. It might be that leisure-time physical activity is enough to improve arterial stiffness but not cardiorespiratory fitness in type 1 diabetic individuals, although no cause and effect relationship cannot be confirmed based on the present study. This might be supported by the finding that in type 1 diabetic subjects leisure-time physical activity was not correlated with VO_{2max} but in control subjects relative VO_{2max} was positively correlated with leisure-time physical activity. Thus, healthy individuals may exercise at higher intensities compared to individuals with type 1 diabetes leading to improvement of cardiorespiratory fitness.

Previous studies investigating the relationship of arterial stiffness and physical activity or aerobic fitness in individuals with type 1 diabetes are scarce but in healthy populations the effect of exercise on arterial stiffness has been studied. In healthy young men CAVI is known to decrease in response to acute low- and moderate-intensity exercise (Wang et al. 2014; Zheng et al. 2015; Zhou et al. 2015) and accumulation of this kind of exercise could lead to chronic improvement of arterial stiffness explaining the found association between leisure-time physical activity and CAVI. A direct effect of exercise on arterial stiffness is supported by the finding that aerobic exercise increases arterial compliance, and the improvement is not associated with maximal aerobic capacity (Tanaka et al. 2000) which would give an explanation why CAVI did not correlate with VO_{2max} in the present study.

Possible mechanisms that would explain the inverse relationship between leisure-time physical activity and CAVI include improved endothelial function and increased NO. Exercise training has been shown to improve endothelium-dependent vasodilatation in coronary and resistance arteries (Hambrecht et al. 2000). In addition, already 150 min/wk of brisk walking has been reported to reduce arterial stiffness, and this reduction was concomitant with increases in NO (Kearney et al. 2014). Exercise may increase shear stress of the endothelium, and shear stress is thought to increase the expression of NO synthase in endothelial cells (Hambrecht et al. 2000). NO then induces relaxation of the vascular smooth muscle leading to the stress to transfer from the stiffer collagen fibers to the more elastic elastin fibers which reduces arterial stiffness (Kearney et al. 2014).

The correlation between CAVI and leisure-time physical activity may be representative of diabetic individuals because no such correlation was found in the control group or when all participant were analyzed as one group. Thus, leisure-time physical activity may be especially important for those with increased risk of cardiovascular diseases. Increasing physical activity could be one way to prevent and slow down arterial stiffening in a risk population like type 1 diabetics.

In healthy adults VO_{2max} has been found to correlate with arterial stiffness (Tanaka et al. 2000) and to have an independent inverse association with progression of arterial stiffness (Gando et al. 2016). That is, those with lower cardiorespiratory fitness have greater risk of arterial stiffening. With lower VO_{2max} type 1 diabetic patients would be at even greater risk because they already seem to have stiffer arteries than healthy controls. However, no such correlation was found in this study suggesting that either cardiorespiratory fitness is not correlated with arterial stiffness in type 1 diabetic individuals or the number of subjects in the present study was too low to show such relationship. It seems possible that CAVI is improved through different mechanisms and independent of changes in cardiorespiratory fitness.

In the level of whole study population there was a moderate but significant negative correlation between absolute VO_{2max} and left CAVI while right CAVI only tended to correlate with VO_{2max}. No correlation was found between relative VO_{2max} and CAVI in the whole study sample. Maximal oxygen uptake was not correlated with CAVI in type 1 diabetes group or the control group. This might suggest that the number of participants in this study was too low to clarify such correlations. This would explain why no correlation was found between relative VO_{2max} and CAVI and why absolute VO_{2max} only tended to correlate with right CAVI.

A negative correlation between CAVI and BMI was found in subjects with type 1 diabetes in the present study. No such correlation was found in the control group or in the level of whole study sample. This finding would suggest that type 1 diabetic individuals with higher BMI, a marker of overweight and obesity, have more favorable CAVI values. Several previous studies have also found an inverse association between CAVI and BMI (Choi et al. 2013; Wang et al. 2013; Tsuboi et al. 2015) while others have not (Kim et al. 2011; Park et al. 2012; Iguchi et al. 2013; Nagayama et al. 2013). Interestingly Namekata et al. (2012) have found a U-shaped association between BMI and CAVI suggesting that individuals with both high and low BMI are at increased risk of having abnormally high CAVI.

Nagayama et al. (2013) have reported a significant positive correlation between CAVI and visceral fat area while CAVI did not correlate with subcutaneous fat area. Also Park et al. (2012) have found that CAVI correlates with visceral and epicardial adipose tissue, which have more atherogenic effects, but not with subcutaneous and total adipose tissue. It seems that adipose tissue in different regions have different effects on artery properties because trunk fat has been shown to be inversely associated but peripheral fat positively associated with large artery stiffness (Ferreira et al. 2004). These findings might suggest that higher body mass itself does not necessarily increase the risk of high CAVI but the distribution of fat would be more relevant in relation to arterial stiffness. It is possible that individuals with type 1 diabetes and low BMI may have more visceral or trunk fat while those with higher BMI may have more subcutaneous or peripheral fat, but this must be confirmed in future studies.

It should be noted that because BMI does not describe body composition those with higher BMI may actually have more muscle mass, not just fat mass, which may have an effect on the correlation between CAVI and BMI. Abbatecola et al. (2012) have found that PWV is inversely associated with peripheral lean mass and skeletal muscle density. Also Ferreira et al. (2004) have reported an inverse association between PWV and peripheral lean mass. In addition, CAVI seems to have an inverse association with muscle mass index (Sampaio et al. 2014). They also found that subjects with lower BMI had lower muscle mass and fat mass index but similar body fat percentage. These findings might suggest that body composition, fat distribution, and muscle mass may have an effect on the relationship between CAVI and BMI. This inverse association may be descriptive of type 1 diabetic individuals, since no correlation between CAVI and BMI was found in the control group. Thus, in individuals with type 1 diabetes BMI may have more importance in relation to arterial stiffness compared to healthy individuals. However, in individuals with type 1 diabetes BMI may not be the best marker but body composition should be taken into account when considering the effect of body mass on arterial stiffness and cardiovascular health.

10.2 Maximal oxygen uptake

In this study type 1 diabetic men without diabetes related complications had lower relative and absolute VO_{2max} compared to matched controls with similar self-reported leisure time physical activity. This in accordance with previous studies (Niranjan et al. 1997; Gusso et al. 2008; Brazeau et al. 2012; Peltonen et al. 2012; Turinese et al. 2017) although some studies have not find a similar difference between individuals with type 1 diabetes and healthy controls (Baldi et al. 2010; Komatsu et al. 2010; Item et al. 2011; Wheatley et al. 2011; Wilson et al. 2017). There was also no association between leisure-time physical activity and VO_{2max} in type 1 diabetes group suggesting that other factors than the amount of physical activity have a greater effect on the aerobic capacity in these individuals. Since maximal aerobic capacity is the product of maximal cardiac output and arterio-venous O_2 difference (Baldi & Hofman 2010) both central and peripheral mechanisms might explain the reduced VO_{2max} in type 1 diabetes.

Several studies have found a lower stroke volume and cardiac output during maximal exercise in type 1 diabetic individuals compared to physical activity matched healthy controls leading to impaired O_2 delivery (Niranjan et al. 1997; Rissanen et al. 2015). A lower blood volume reported in type 1 diabetics probably contributes to decreased maximal cardiac output by reducing ventricular preload (Koponen et al. 2013; Rissanen et al. 2015). Also decreased maximal heart rate, especially in type 1 diabetic individuals with poor glycemic control, may affect the reduced cardiac output suggesting autonomic dysfunction as a limiting factor of aerobic capacity (Niranjan et al. 1997; Veves et al. 1997; Baldi et al. 2010).

Also reduced pulmonary diffusion has been offered as an explanation for lower VO_{2max} in type 1 diabetes (Niranjan et al. 1997; Wheatley et al. 2011). Wheatley et al. (2011) found a reduced lung diffusing capacity in athletes with type 1 diabetes compared to controls. When the diabetic group was further divided according to glycemic control (HbA1c) it was found

that subjects with poor glycemic control had alveolar-capillary membrane conductance and reduced lung diffusing capacity compared to subjects with optimal glycemic control. Although a positive correlation between lung diffusing capacity and peripheral O_2 saturation was found, no reduction in peripheral O_2 saturation during peak exercise was observed in type 1 diabetic subjects compared to controls. (Wheatley et al. 2011.) Also Niranjan et al. (1997) have reported a decreased membrane diffusing capacity and pulmonary capillary blood volume during heavy exercise in hyperglycemic type 1 diabetic individuals compared to healthy controls. Even though it seems that pulmonary diffusion is reduced in type 1 diabetes, it should be noted that any diabetes-related arterial hypoxemia during exercise is likely too modest to cause seriously reduced oxygen transport and consumption at low altitude (Baldi & Hofman 2010).

In addition to arterial O_2 saturation, distribution of blood flow to working tissues and peripheral oxygen extraction can also affect arterio-venous O_2 difference (Baldi & Hofman 2010). Decreased blood flow in working muscle during exercise has been reported in individuals with type 1 diabetes suggesting altered muscle perfusion in maximal exercise possibly due to peripheral vascular dysfunction and/or functional alterations in the microcirculation (Rissanen et al. 2015; Tagougui et al. 2015). This is further supported by the finding of increased systemic vascular resistance at peak exercise in type 1 diabetic subjects (Baldi et al. 2010; Rissanen et al. 2015). Nitric oxide may play part in this because endothelium-derived NO is considered essential in maintaining an adequate vascular response to increased blood flow demands during exercise (Hambrecht et al. 2000).

Also a blunted increase in deoxyhemoglobin found in type 1 diabetics with poor glycemic control and a positive correlation between VO_{2max} and change in deoxyhemoglobin support the idea of suboptimal blood flow distribution as a limiting factor of aerobic capacity, although they can also be manifestations of reduced capacity of tissue to use oxygen as in mitochondrial dysfunction (Tagougui et al. 2015). However, the influence of mitochondrial dysfunction on VO_{2max} in type 1 diabetes seems equivocal since some studies have not found any change in mitochondrial capacity (Item et al. 2011) while some have reported

reduced oxidative capacity (Crowther et al. 2013) in type 1 diabetic individuals. Also the higher affinity of glycosylated hemoglobin to oxygen (Ditzel 1976) may limit the extraction of O_2 although studies reporting no difference in arterio-venous O_2 difference do not support this assumption (Item et al. 2011; Rissanen et al. 2015).

In this study glycemic control presented as HbA1c was not associated with $VO_{2max,}$ which is supported by some (Peltonen et al. 2012; Rissanen et al. 2015; Turinese et al. 2017; Wilson et al. 2017) but not all (Veves et al. 1997) studies. Previous studies have reported that HbA1c is correlated negatively with peak stroke volume (Baldi et al. 2010; Rissanen et al. 2015), peak cardiac output (Item et al. 2011; Rissanen et al. 2015), mitochondrial capacity (Item et al. 2011), lung diffusing capacity, and alveolar-capillary membrane conductance (Wheatley et al. 2011). Although a negative correlation between HbA1c and training volume has been reported (Baldi et al. 2010), it seems that glycemic control has a more powerful effect on aerobic exercise capacity than exercise training has on glycemic control in subjects with type 1 diabetes (Baldi & Hofman 2010). This is supported by the finding that in type 1 diabetic subjects with similar training status those with poor glycemic control have lower VO_{2max} than those with optimal glycemic control (< 7%) (Niranjan et al. 1997; Baldi et al. 2010; Tagougui et al. 2015). Therefore it has been proposed that to achieve the same aerobic capacity as nondiabetic individuals, maintaining good glycemic control may be necessary for individuals with type 1 diabetes (Baldi & Hofman 2010).

Taken together, it appears that even if glycemic control does not have a direct link to aerobic capacity, components of VO_{2max} seem to be associated with HbA1c. As the mean HbA1c of type 1 diabetic subjects in this study (7.5%±0.7) was somewhat higher than the goal of <7% (American Diabetes Association 2016) and more specifically only 3 out of 11 diabetic subjects had adequate glycemic control, it may be that slightly impaired glycemic control has contributed to reduced VO_{2max} of type 1 diabetic subjects in this study. Since HbA1c is associated with stroke volume and cardiac output (Baldi et al. 2010; Item et al. 2011; Rissanen et al. 2015) it is possible that reduced cardiac performance has limited the maximal aerobic capacity of subjects with type 1 diabetes in this study.

It must be taken into account that leisure-time physical activity in this study was reported as minutes per week. That is, only volume but not intensity of physical activity was considered in the questionnaire. Since lower ventilatory thresholds have been reported in type 1 diabetic individuals (Komatsu et al. 2010; Peltonen et al. 2012) it may be that they consciously or unconsciously choose to exercise at lower intensities that probably feel more comfortable. Thus, the intensity of physical activity in type 1 diabetic subjects may have been lower than in control subjects and, in spite of similar volume, not enough to elicit increases in VO_{2max}.

10.3 ABI

There was no difference in ABI between the type 1 diabetic men and healthy controls as was hypothesized. No association between ABI and HbA1c or duration of diabetes was found. Both in the T1D group and control group ABI was rather high (1.1 for both groups and both sides) when ABI values of <0.9 are usually considered to indicate peripheral arterial disease (PAD) (Potier et al. 2011). The ABI value of both groups in this study would be classified as normal since ABI values of 0.91–1.30 are generally considered normal (Hiatt 2001; Potier et al. 2011) although also a higher normal ABI range of 1.11–1.40 has been proposed (Ankle Brachial Index Collaboration 2008).

Previous studies comparing ABI in type 1 diabetic and nondiabetic individuals are very limited. In a mixed group of type 1 and type 2 diabetic subjects ABI was not different compared to nondiabetic controls (Ibata et al. 2013). Forbang et al. (2014) reported no difference in ABI between type 2 diabetic subjects without PAD and subjects without diabetes and PAD with ABI values similar as found in this study. Tehan et al. (2016) also found no difference in ABI between elderly diabetic and nondiabetic subjects. Similar ABI values have also been found in elderly diabetic men (Maeda et al. 2008) and type 2 diabetic individuals (Gómez-Marcos et al. 2015). Thus, ABI seems to be similar in young type 1 diabetic men compared to healthy controls.

The interpretation of ABI in individuals with diabetes may sometimes be challenging. The medial artery calcification highly prevalent in diabetic individuals leads to poorly compressible vessels and falsely high ABI. Therefore normal ABI values may not always be enough to rule out the diagnosis of PAD in individuals with type 1 diabetes. (Potier et al. 2011.) Ix et al. (2012) have reported that 48% of young type 1 diabetic subjects with ABI 0.90–1.30 had MAC on X-ray imaging, which questions the sensitivity of ABI. It should be noted that in the study by Ix et al. (2012) 13% of subjects had cardiovascular disease, 21% had hypertension and the average duration of diabetes was 10 years longer than in this study.

The type 1 diabetic subjects in this study did not have any diabetes related complications and were relatively young, thus a normal ABI would be expected. However, duration of diabetes over 10 years is considered to be a risk factor for PAD (American Diabetes Association 2003), and the average duration of T1D in this study was 13±7 years suggesting increased risk of PAD in this group. When normal or high values of ABI cannot always rule out the possibility of PAD (Potier et al. 2011) and a high likelihood of false negative results has been reported (Tehan et al. 2016) the possibility of PAD in these type 1 diabetic subjects cannot be completely excluded. Nevertheless, the absence of diabetic complications in these subjects would suggest the ABI value to be reliable.

ABI was not found to be correlated with VO_{2max} or leisure-time physical activity in the type 1 diabetes group, control group, or in the whole study sample. These findings are not supported by previous studies. Leisure-time physical activity has been shown to be positively correlated with ABI both in healthy individuals and in individuals with PAD (Ruiz Comellas et al. 2015). In patients with intermittent claudication peak oxygen uptake has been reported to be higher in subjects with higher ABI than in subjects with lower ABI (Gardner & Clancy 2006).

A positive correlation between ABI and VO_{2max} as well as ABI and leisure-time physical activity could be expected although the causal relationship is not clear. On one hand low ABI is indicative of PAD (Potier et al. 2011) which may lead to intermittent claudication causing pain when walking (American Diabetes Association 2003). This pain would very likely limit physical activity and the intensity of exercise making it difficult to maintain or improve cardiorespiratory fitness. On the other hand, physical activity has anti-atherogenic effects and it reduces the levels of several key factors in the atherosclerosis process (Palmefors et al. 2014). In this study the number of participants may have been too small to observe a correlation between ABI and leisure-time physical activity and ABI and VO_{2max}. It may also be that in young men with normal ABI leisure-time physical activity and VO_{2max} are not associated with ABI.

10.4 Blood pressure at rest

No difference in diastolic and systolic blood pressure, mean arterial pressure and pulse pressure at rest was found between type 1 diabetic men and healthy controls. This is consistent with previous studies (Kool et al. 1995; Berry et al. 1999; Wilkinson et al. 2000) although some studies have found increased blood pressure and pulse pressure in type 1 diabetic subjects (Brooks et al. 1999; Rönnback et al. 2004). CAVI was found to be negatively correlated with pulse pressure in type 1 diabetes group but not in control group or in the whole study sample. No correlation between CAVI and systolic blood pressure, diastolic blood pressure or mean arterial pressure in any of the groups was found.

Previous studies have reported inconsistent findings. Several studies have not found CAVI to be correlated with systolic and diastolic blood pressure (Ibata et al. 2008; Horinaka et al. 2011; Choi et al. 2013; Tanisawa et al. 2015) while some have (Nagayama et al. 2013; Wang et al. 2013; Tsuboi et al. 2015). Choi et al. (2013) have reported also no correlation between CAVI and mean arterial pressure. Since CAVI is independent of blood pressure

(Shirai et al. 2011b) and the participants of the present study were mainly normotensive, the absence of correlation between CAVI and blood pressure is not surprising.

Although no differences was yet found in blood pressure the subclinically elevated arterial stiffness in type 1 diabetic subjects may represent an increased risk to develop cardiovascular disease and hypertension. If arterial stiffness keeps increasing as normally happens with aging it progressively leads to increased PWV and earlier wave reflection causing augmentation of systolic blood pressure and increased cardiac workload (Brooks et al. 1999). This arterial stiffening may reach pathological state faster in individuals with type 1 diabetes if they already have higher arterial stiffness than healthy individuals.

The correlation between CAVI and pulse pressure found in type 1 diabetic subjects was inverse suggesting that higher pulse pressure, which is mainly determined by arterial stiffness (Ni et al. 2003) is associated with lower CAVI representing lower arterial stiffness. Previous studies have shown a positive correlation between CAVI and pulse pressure (Kim et al. 2011; Wang et al. 2013) or no correlation (Choi et al. 2013). Also Ni et al. (2003) have reported a positive relationship between PWV and pulse pressure. An increase in PWV, which is a marker of arterial stiffness, would result in earlier wave reflection return to the aorta and increased systolic blood pressure and pulse pressure as diastolic blood pressure decreases (Ni et al. 2003). The negative correlation between CAVI and pulse pressure found in the present study is conflicting with previous studies and illogical itself. Since no correlation between CAVI and pulse pressure was found in the control group or when all participants were analyzed as one group, it may be that the inverse correlation found in type 1 diabetes group was just coincidence in this group of participants and cannot be applied into larger scale.

In addition to CAVI pulse pressure was negatively correlated with ABI in type 1 diabetic subjects, but not in the control group. This is in line with previous studies reporting inverse association between ABI and pulse pressure in elderly individuals with arteriosclerosis (Li

et al. 2006) and in elderly subjects without stroke and coronary heart disease (Zhan et al. 2012). With every 5 mmHg increase in pulse pressure the risk of low ABI has been found to increase by 19 % and 10 % in men and women, respectively (Zhan et al. 2012). Thus, in individuals with type 1 diabetes ABI and pulse pressure seem to be closely related indicating that when one of them increases the other is also likely to increase.

In type 1 diabetes group and in the whole study sample, but not in the control group, absolute VO_{2max} was found to be positively correlated with systolic blood pressure, diastolic blood pressure and mean arterial pressure. However, leisure-time physical activity or relative VO_{2max} was not correlated with any of the blood pressure measures in any of the groups. The positive correlation between VO_{2max} and blood pressure, suggesting that having higher cardiorespiratory fitness is associated with higher blood pressure, is opposite of what is known about the relationship between exercise and blood pressure based on previous research.

There is strong evidence that regular exercise or a chronic increase in physical activity leading to increased cardiorespiratory fitness attenuates the age-related progressive increase in blood pressure preventing hypertension. In individuals with hypertension regular physical activity lowers blood pressure independent of other risk factors. Causal mechanisms are supported by the dose–response relationship between increased cardiorespiratory fitness, blood pressure, and mortality risk reduction. (Kokkinos 2014.)

Absolute VO_{2max} usually is not the best indicator of cardiorespiratory fitness because it does not take individual's body mass into account. That is, two individuals with different body mass may have similar absolute VO_{2max} but very different capacity to perform aerobic exercise. Therefore the correlation between absolute VO_{2max} and blood pressure cannot be directly interpreted to indicate positive association between cardiorespiratory fitness and blood pressure.

Individuals with greater body mass and BMI may have higher absolute VO_{2max} than individuals with lighter body mass despite lower relative VO_{2max}. The inverse association between BMI and CAVI may give one possible explanation why absolute but not relative VO_{2max} was found to be negatively correlated with CAVI. Although no correlation between absolute VO_{2max} and blood pressure measures was found in the present study, previous research have reported positive correlation between BMI and blood pressure (Wu et al. 2017) as well as between adiposity and blood pressure (Doll et al. 2002). It may be that the unusual finding of positive correlation between VO_{2max} and blood pressure is partly explained by higher body mass index leading to higher absolute VO_{2max} and higher blood pressure.

10.5 Limitations of the study

This study has several limitations. First, the number of participants was quite small and studies with larger number of participants are needed to confirm the findings of the present study. The type 1 diabetic subjects were also without diabetic complications and relatively young, thus the findings might not be possible to apply to different populations. Second, leisure-time physical activity was assessed through physical activity questionnaires. Only the duration of leisure-time physical activity was reported but the intensity was not taken into account which might have given more information about the factors associated with arterial stiffness. Leisure-time physical activity was self-reported and reporting bias may have affected the results. Using accelerometers might provide additional and more reliable information in this regard.

This study was a cross-sectional study, thus any conclusions in regard to causal relationships cannot be made. Longitudinal studies are needed in the future to investigate if higher levels of physical activity or cardiorespiratory fitness protect type 1 diabetic individuals from arterial stiffening and if increased arterial stiffness can be normalized or improved through exercise.

10.6 Conclusions

In conclusion arterial stiffness young men with type 1 diabetes was found to be subclinically increased. This would implicate increased risk for premature arterial stiffening. In type 1 diabetic subjects higher leisure-time physical activity was associated with lower arterial stiffness suggesting that spending more time being physically active may be beneficial in terms of arterial stiffness. Since the association between leisure-time physical activity and arterial stiffness was not found in the control group the results would suggest that physical activity during leisure time may be especially important for individuals with type 1 diabetes.

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