Thesis

Effects of maximal cardiopulmonary exercise (CPX) testing on micro- and macrovasculature in people with type 1 diabetes

submitted by

Vincent Jander

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Univ.-Prof. Priv.-Doz. Mag. Dr. Othmar Moser und
Dr. BSc MSc Max Lennart Eckstein

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Affirmation under oath

I hereby declare under oath, that I have written the present thesis independently and without external help, that I have not used sources other than the listed, and that I have marked all passages that were quoted directly or contentual.

Nuremberg, November 24, 2021 *Vincent Jander eh.*

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Abbreviations

T1D	Type 1 diabetes
T2D	Type 2 diabetes
CGM	Continuous glucose monitoring
CVD	Cardiovascular disease
ADMA	Asymmetric dimethylarginine
PWV	Pulse wave velocity
cfPWV	Carotid femoral pulse wave velocity
SVA	Static retinal vessel analysis
CRAE	Central retinal arteriolar equivalent
CRVE	Central retinal venular equivalent
AVR	Arteriolar-to-venular diameter ratio
NT-proBNP	N-Terminal pro-B-type natriuretic peptide
IL-6	Interleukin 6
NO	Nitric oxide
PA	Physical activity
CRF	Cardiorespiratory fitness
tCPX	Exercise duration of mCPX
HbA$_{1C}$	Haemoglobin A$_{1c}$
MD	Mean difference

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Abstract in German

Einleitung

Für diese Diplomarbeit wurden die direkten Auswirkungen eines maximalen kardiopulmonalen Belastungstest (mCPX-test) auf das Mikro- und Makrogefäßsystems von Typ 1 Diabetiker*Innen untersucht. Repräsentativ für das Gefäßsystem wurden asymmetrisches Dimethylarginin (ADMA), Pulswellengeschwindigkeit (PWV), Interleukin-6 (IL-6), N-Terminales pro-B-Typ natriuretisches Peptid (NT-proBNP), zentrales retinales arterioläres Äquivalent (CRAE), zentrales retinales venuläres Äquivalent (CRVE) und das retinale Verhältnis von Arteriole zu Venole (AVR) bestimmt. Zusätzlich wurde der Effekt von kardiorespiratorischer Fitness (CRF) auf Mikro- und Makrovaskuläre Veränderungen von Menschen mit Typ 1 Diabetes (T1D) erörtert. Hierfür untersuchten wir die Korrelation zwischen den genannten Gefäßmarkern und der CRF der Proband*Innen. Außerdem wurden Merkmale der diabetischen Erkrankung (Dauer der Diabetes-erkrankung, C-Peptid, tägliche Gesamtdosis an Insulin pro Körpergewicht, HbA1C), Ergebnisse der mCPX (mittlere Glucose- und Laktatkonzentrationen während der mCPX, Dauer der mCPX und VO2max) und allgemeine Charakteristika (BMI, Geschlecht und Alter) gruppiert und anschließend mit den Gefäßmarkern verglichen. So war diese Arbeit erkenntnisleitend hinsichtlich der Art und des Ausmaßes des Einflusses klinisch-erkrankungsspezifischer Charakteristika von T1D auf die Belastungsadaptation des Gefäßsystems, sowie dessen Gesundheitszustand.

Methodik

Fünf weibliche und fünf männliche, sportlich aktive Teilnehmer*Innen mit T1D absolvierten einen stufenweise, bis zur maximalen Erschöpfung durchgeführten, Ausdauerbelastungstest (mCPX) auf einem Fahrradergometer. Die individuelle Fitness wurde dabei durch spirometrische Gasaustauschmessung ermittelt und als VO2max [mL*kg-1*min-1] dargestellt. IL-6, NT-proBNP, ADMA, PWV und die retinalen Bilder wurden unmittelbar vor (T0), unmittelbar nach (T1) und 30 min (T2), 60 min (T3) und, wenn zutreffend, 24 Stunden (T4) nach dem CPX-test gemessen. Vor und während der mCPX wurden die persönlichen Merkmale, die individuellen Charakteristika der diabetischen Erkrankung und in regelmäßigen Abständen die Blutkonzentrationen von Glucose und Laktat bestimmt.

Ergebnisse

NT-proBNP (p = 0,010) und IL-6 (p = 0,023) zeigten direkt nach der mCPX einen signifikanten Anstieg, während ADMA (p = 0,011) signifikant abfiel. Für PWV, AVR, CRAE und CRVE waren keine signifikanten (p > 0,05) Unterschiede zwischen T0 und den anderen Messzeitpunkten festzustellen.

In der linearen Regressionsanalyse konnte keine signifikante (p > 0,05) Korrelation zwischen VO2max und den untersuchten vaskulären Markern gezeigt werden. Allerdings wurde eine signifikante inverse Korrelation (p(two tailed) = 0,0092; r2 = 0,59) zwischen VO2max und der Konzentrationsänderung von ADMA zwischen T0 und T1 festgestellt. Zwischen der Gruppe, mit nachweisbarem C-Peptid-Konzentrationen und der ohne nachweisbares C-Peptid zeigte sich ein signifikanter Unterschied der PWV (adj. p = 0,020) bei T0, sowie des NT-proBNP (adj. p = 0,030) bei T1.

Das Gruppieren nach Geschlecht ergab signifikant höhere IL-6 Konzentrationen bei den weiblichen Teilnehmer*Innen zum Zeitpunkt T0. Das Gruppieren nach Diabetesdauer, der täglichen Gesamtdosis an Insulin pro Körpergewicht, des HbA1C, des BMI und des Alters ergab keine signifikanten Unterschiede (p > 0,05). AVR zum Zeitpunkt T3 korrelierte signifikant mit der Dauer der mCPX (p = 0,032; r2 = 0,82) und den mittleren Glucosekonzentrationen während der mCPX (p = 0,047; r2 = 0,78).

Zusammenfassung

Die Ergebnisse legen einerseits die vorteilhaften Auswirkungen der mCPX auf IL-6, NT-proBNP und ADMA dar und unterstreichen andererseits die problematischen Effekte von körperlicher Belastung bei Menschen mit T1D. PWV und das retinale Gefäßkaliber wurden, anders als in Forschungsergebnissen an gesunden Proband*Innen, nicht signifikant von der mCPX beeinflusst.

Die meisten Parameter korrelierten nicht mit dem Anstieg oder Abfall der vaskulären Marker, was darauf schließen lässt, dass Menschen mit T1D von der CPX unabhängig von ihrer CRF profitieren können. Die VO2max korrelierte mit der Differenz der ADMA zwischen T0 und T1 was zeigt, dass bei Menschen mit T1D, durch eine Erhöhung der CRF die intakte trainingsinduzierte ADMA-abhängige Vasoregulation aufrechterhalten werden kann. Ähnlich zu vorhergehenden Publikationen, konnten auch wir ein höheres Ruhe-IL-6 bei Frauen, im Vergleich zu Männern, beobachten. Nach der mCPX konnte eine Annäherung der IL-6 Werte zwischen Männern und Frauen beobachtet werden, was eine Unterschiedliche Reaktion des Parameters auf den Belastungsreiz nahelegt. Ein signifikanter Abfall des NT-proBNP und der PWV in der Gruppe mit nachweisbarer C-peptid-Sekretion zeigt einen positiven Effekt einer Insulin-Restsekretion auf das Myokard und das Epithel der Aorta.

Abstract in English

Introduction

For this thesis, we investigated the reaction of the micro- and macrovasculature in Type 1 Diabetes (T1D) to maximum cardiopulmonary exercise (mCPX) testing by representatively measuring asymmetric dimethylarginine (ADMA), pulse wave velocity (PWV), interleukin-6 (IL-6), N-terminal pro-B-type natriuretic peptide (NT-proBNP), central retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE) and arteriolar-to-venular diameter ratio (AVR). Additionally, we aimed to analyse the effect of cardiorespiratory fitness (CRF) on microvascular and macrovascular alterations. This was achieved by analysing the correlation between the vasculature-markers and CRF of the study participants. Furthermore, diabetic disease characteristics (diabetes duration, C-peptide, total daily dose of insulin, HbA1C), mCPX-results (mean glucose and lactate concentrations during mCPX, duration of mCPX (tCPX) and VO2max) and subject characteristics (BMI, sex, age) were respectively grouped and subsequently compared to the vasculature-markers. Thereby we were able to gain a better understanding on how, and to what extent, these characteristics, that are all important in the clinical disease evaluation of people with T1D, influence vascular exercise responsiveness and health.

Material and Methods

Five female and five male physically active participants with T1D underwent a maximal incremental exercise test using a cycle ergometer. The individual fitness was depicted as VO_{2max} [mL*kg-1*min-1], which was acquired from spirometric gas-exchange measurements. IL-6, NT-proBNP, ADMA, PWV, and retinal imaging were measured immediately before (T0), immediately after (T1) and 30 min (T2), 60 min (T3), and, if applicable, 24 h (T4) after the CPX testing. Before and during mCPX, the participants personal and diabetic disease characteristics were determined, and glucose and lactate concentrations were periodically measured.

Results

NT-proBNP ($p = 0.010$) and IL-6 ($p = 0.023$) both showed a significant increase while ADMA ($p = 0.011$) was significantly decreased following mCPX. There was no significant difference in PWV, AVR, CRAE and CRVE between T0 and the other timepoints. The linear regression analysis did not show a significant ($p > 0.05$) correlation between VO2max and any of the investigated vasculature parameters at the timepoints. However,

there was a significant (p(two tailed) = 0.0092; r2=0.59) inverse correlation betweenVO2max and change of ADMA concentrations from T0 to T1. The grouped analysis of the parameters showed a significant difference (adjusted p-value = 0.020) between PWV of the group with detectable C-peptide and the group that had no detectable C-peptide secretion at T0 and a significant difference (adjusted p value = 0.030) between the NT-proBNP values of the C-peptide groups at T1 was found. The grouping by sex revealed a significantly (adjusted p-value = 0.00006) elevated IL-6 concentration in females at T0. The grouping by diabetes duration, TDD/kg, HbA1C, BMI and age did not show significant (p > 0.05) differences.

AVR showed a significant correlation with tCPX (p = 0.032; r2 = 0.82) and with mean glucose concentrations at T3 (p = 0.047; r2 = 0.78). The other parameters did not correlate significantly (p > 0.05) with the duration of mCPX, mean glucose concentrations or mean lactate concentrations at any of the time points.

Conclusion

The results show a clear beneficial effect of mCPX on IL-6, NT-proBNP and ADMA, while underlining the ambiguous effects of CPX in T1D. PWV and retinal vessel calibres were, differently than results in healthy subjects, not significantly influenced by mCPX. The change of most of the parameters was not associated with CRF, implying that people with T1D benefit from CPX independently of their exercise capacity.

We found a positive correlation between VO2max and change in ADMA concentration between pre- to post mCPX showing that individuals with T1D can exercise induced ADMA-dependent vasoregulation elevated CRF profit more from. Similar to previous reportings, we found a higher pre-exercise IL-6 in women compared to men. After mCPX an alignment of the parameter between men and women could be observed, indicating different stimulus-reaction in men and women with T1D. A significant reduction in NT-proBNP and PWV in the group with detectable C-peptide hints toward a positive effect of obtained insulin secretion on the myocardium and aortal endothelium.

1 Introduction

1.1 Epidemiology of diabetes

Diabetes is a worldwide epidemic that has reached an alarming extent. According to the ninth version of the International Diabetes Federation *Diabetes Atlas*, an estimated almost 500 million people have diabetes worldwide, and this number is increasing every year. Type 1 Diabetes (T1D) accounts for approximately 5–10% of all diabetes cases (1). The annual incidence of T1D showed an increase in the United States of America (2) and European countries (3) over the past decades. An 2–5% worldwide increase in the incidence of diabetes and an increase in prevalence can be observed, and the greatest increase in incidence can be seen among children (4,5).

1.2 Differentiation between type 1 diabetes and type 2 diabetes

Even though T1D and Type 2 Diabetes (T2D) are both defined by chronic hyperglycaemia, the pathophysiological processes that lead to elevated blood glucose differ. The main difference is the amount of insulin produced. T2D is characterised by both the resistance of tissues to insulin and impaired insulin secretion, which lead to altered glucose homeostasis performance in peripheral tissues (6).

Differently, T1D is a cellular-mediated chronic autoimmune disease that manifests as the loss of the β-cells in the pancreatic islands (7). The exact mechanisms of the destruction of insulin-secreting cells is still subject of ongoing research, and these mechanisms are seen as involving the complex interplay between many factors (7). Usually, T1D leads to a progressive decline in insulin production and, eventually, to a functional absence of insulin in the body, resulting in lifelong dependency on insulin substitution for people with T1D (7). Despite the β-cell loss, even people with long-term T1D still have residual insulin-secreting cells and a minimum of one third can be called insulin microsecreters with detectable C-peptide, which is produced in equimolar amounts to insulin (7,8).

Although insulin resistance is viewed as a key pathophysiological process in people with T2D (9), it is also found in adolescents and adults with T1D and is associated with increased incidence of CVD and mortality (10). Higher daily insulin dose per kilogram of bodyweight, suggestive of higher insulin resistance, increases the risk of coronary artery calcification (11).

1.3 Management of T1D

Almost 100 years after Banting and Best were able to successfully isolate insulin and demonstrate its efficacy in diabetes treatment, a cure for this chronic condition is still not available (12). When it was first introduced, insulin treatment emerged as a game-changer and meant that T1D no longer had to be considered an inevitable and prompt death sentence. However, the prolonged duration of the disease brought up new kinds of chronic vascular complications that develop in the long term (12). In the face of these new challenges, another milestone in the management of T1D was reached in 1993. The Diabetes Control and Complication Trial and its follow-up were able to show that microvascular and cardiovascular complications are preventable by consistently keeping the glucose level as close as possible to physiological glycaemic ranges (13,14). To achieve this goal, a lifelong self-managed lifestyle concept that includes glucose monitoring, insulin therapy, dietary measures with carbohydrate counting and physical activity must be implemented (15).

Today, the insulin regimen usually consists of basal insulin dosing and application of bolus doses of rapid-acting insulin either via continuous subcutaneous insulin infusion (CSII) or multiple daily injections to emulate physiologic insulin levels (12, 13). If the applied dosage is adequate, then must be frequently checked using either repeated capillary blood glucose measurement or continuous glucose monitoring (CGM) devices. Metabolic control is mandatory to prevent acute potentially life-threatening conditions caused by severe hypoglycaemia (namely ketoacidosis and hypoglycaemia), on the one hand, and crucial in preventing chronic microvascular and macrovascular conditions that can lead to further complications and death, on the other hand (18).

1.4 Cardiovascular complications and mortality in T1D

Acute metabolic complications are the leading cause of death among young people with T1D (19). With the progression of the disease, however, chronic cardiovascular, renal and infectious complications become increasingly frequent (20). Because T1D leads to accelerated and severe atherosclerosis and endothelial dysfunction, cardiovascular disease (CVD) is the leading cause of premature morbidity and mortality for the people affected by it (16, 17). In past years, the burdens of CVD mortality and all-cause mortality have been reduced (22) as advancements in the management of T1D have been made. These advancements include the aforementioned improvements in technology to support individual glucose management, like CGM, improved insulin delivery, enhanced insulin application regimens and updated patient education (12). Despite this positive development, individuals affected by T1D still have, apart from a massively increased risk of all-cause mortality and CVD mortality (18,23), a considerably shortened life expectancy compared to the general population (24,25). Even though CVD primarily affects middle-aged or elderly populations, the atherosclerotic changes that are the primary cause of CVD start sooner in life, and endothelial impairment can be detected early in T1D patients, even before subjects show clinical or subclinical signs of (premature) vascular complications (26,27). Generally, these conditions can be grouped, regarding the affected tissues, into microvascular and macrovascular complications.

1.4.1 Microvascular disease in T1D

Microvascular complications in T1D predominantly appear as retinopathy, neuropathy, and nephropathy, but they can also impair cognitive, cardiac and other organic functions (7). As demonstrated in the Diabetes Control and Complications Trial, these complications are a result of chronic hyperglycaemia and are associated with elevated levels of HbA_{1C} (28) and can be addressed through optimal glycaemic management (28). The incidence of microvascular complications can be vastly reduced, and progression can be stalled, especially when intensive treatment is implemented in the early stages of the disease. Despite the beneficial effects of intensive glucose management, the HbA_{1C} value is unable to solely explain inter-individual differences in the rate and severity of these complications. Daily fluctuations, as well as the visit-to-visit variability of HbA_{1C} seem to have additional predictive value in microvascular disease development (29).

1.4.2 Macrovascular complications in T1D

The macrovascular complications that can occur with T1D include heart disease, stroke and peripheral arterial disease caused by atherosclerosis and thrombosis. The development of microvascular and macrovascular complications are strongly interconnected (30). Exemplarily, diabetic nephropathy induces the risk of macrovascular complications, forming an interplay between microvascular and macrovascular disease in T1D patients (31). But other than microvascular disease, macrovascular complications do not seem to be as strikingly changeable by intensive glycaemic management (7). However, thanks to improved glycaemic control and the management of associated risk factors, the risk of developing microvascular and macrovascular complications has decreased among T1D patients, and outcomes were improved in recent decades (32,33).

1.5 Physical activity, exercise and T1D

1.5.1 Positive effects of exercise

Exercise is used as a tool to obtain, sustain, or improve physical fitness by exploiting structured activities. This is achieved by raising the metabolic activity of the muscles to evoke an adaptive response of the cardiovascular, respiratory, and metabolic systems. Physical activity has proven to significantly lower the risk of CVD and is associated with reduced mortality risk in healthy individuals and individuals with T2D (34,35). Furthermore, individuals benefit from physical exercise because it improves their overall quality of life (36) and has potentially positive effects on multiple chronic diseases, such as obesity, CVD, osteoporosis, osteoarthritis clinical depression, and certain types of cancer (37). Sedentary behaviour, on the contrary, increases the risk of all-cause mortality, CVD-mortality, and cancer mortality (38).

These are all reasons to universally recommend and encourage physical activity (PA) to the general population, including people with diabetes. However, the impact of PA on people affected by T1D and how these positive effects are transferable to individuals with the disease have not been conclusively clarified. On the one hand, it has been reported that high aerobic capacity is associated with high levels of HbA_{1C} in people with T1D, which could indicate that they have poor glycaemic regulation during and after PA (39). It is often feared that this could promote the emergence of diabetic complications. On the other hand, several researchers have demonstrated that there is an inverse relationship between PA and diabetes-related complications and comorbidities, including the prevalence of microvascular (40) and macrovascular complications (41,42). Physically active individuals suffer less commonly and less severely from complications associated with T1D (40,43) and have a longer life expectancy than others (41,44). Additionally, physically active people with T1D have an overall improved quality of life (45) and reduced risk of all-cause mortality (46,47) and cancer (48).

1.5.2 Physiology of exercise in healthy individuals

Among healthy individuals, exercise provokes major changes in the provision and utilisation of glucose. To maintain euglycemia throughout physical strain, the elevated glucose demand is met by upregulating glucose mobilisation and production (49). This response is regulated by circulating insulin, glucagon, catecholamines, cortisol, and growth hormones (50). Physical exercise induces the translocation of insulin-dependent and -

independent glucose transporters like GLUT 4 (51). Thereby, exercised skeletal muscles are provided with increased glucose uptake. Insulin sensitivity is elevated through regular exercise training as well as single aerobic exercise bouts (49,52,53). This increased sensitivity is compensated for through the reduction of endogenous insulin production (54).

1.5.3 Physiology of exercise in T1D

Apart from an increased risk of acute hypoglycaemic events during and after exercise, the central and peripheral hemodynamic response to PA among T1D patients has been described to be altered (55). When responding to exercise, people with T1D have a lower maximum heart rate (HR_{max}) and stroke volume, resulting in low cardiac output (56), even when they are asymptomatic (57). Additionally, exercise performance is negatively affected by T1D because muscular blood flow (58), pulmonary diffusing capacity and overall pulmonary function seem to be progressively impaired as diabetes progresses and with time spent in hyperglycaemic states (57,59,60). Additionally, the results of a recent study on young individuals with T1D revealed that respiratory capacity and microvascular reactivity to physical activity is altered in the muscles, which could disturb oxygen delivery during aerobic exercise (61). Nevertheless, performing PA comes with improvements in lipid levels and endothelial function (62). Additionally, it lowers insulin requirements and insulin resistance (62) and can prolong the so-called honeymoon period, thereby delaying early T1D development (63).

1.5.4 Exercise recommendations

Concerning the above-mentioned positive aspects of physical activity, and to prevent the potential vascular complications in T1D, the American Diabetes Association recommends at least 150 min of moderate-to-vigorous exercise per week to most adults with diabetes (64). Exercise provides a simple and holistic addition to conventional treatment that can, in combination with pharmaceutical and technological therapies, prevent and improve complications in T1D. Clinical routine exercise is typically prescribed to patients as a general recommendation rather than a supervised exercise intervention because it involves relatively less cost and time expenditures (65). For optimal glycaemic control, the American Diabetes Association suggests a target HbA_{1C} for adults that have diabetes of less than 53 mmol/mol (7.0 %), as it is associated with a reduction in rate of development and progression of diabetic microvascular complications compared to higher HbA_{1C} (66).

1.5.5 Glycaemic management during and after exercise

Unfortunately, in T1D, the mechanisms of glucose homeostasis are blunted and the response to exercise is altered, causing the possibility of hypoglycaemic events among affected individuals. This risk is promoted by an interplay between altered insulin sensitivity level and increased insulin absorption and provision (67,68). Because insulin levels cannot be quickly reduced during physical strain as they can in healthy individuals, excessive blood levels of insulin, concerning glucose utilisation, often lead to hypoglycaemia during or after exercising (69). Meanwhile, lack of insulin may induce hyperglycaemia or ketosis (50). The absence of the function of pancreatic-islet β-cells makes every exercise sessions be accompanied by a unique set of challenges that must be addressed through precise planning and scheduling (70).

Although newly improved glucose management technologies like CGM, advanced patient education and continuous subcutaneous insulin infusion support people with T1D to practice different disciplines of physical activity and even take part in competitive sports (71–74), patients are still left to self-manage the exercise recommendations in their daily lives, and many people affected by T1D lack an adequate level of physical fitness (75). This can partially be attributed to fear of hypoglycaemia and loss of glycaemic control (76). One feared complication of exercise is the occurrence of late-onset hypoglycaemia, which can commonly happen 6 to 15 hours after both endurance and anaerobic exercise and can cause serious complications (77). Early in disease development, the body's response when entering hypoglycaemic ranges, in most cases, is to adequately activate the sympathoadrenal neurohumoral response to restore euglycemia (50). This response involves behavioural defences that cause neurogenic symptoms (78). Unfortunately, in more progressed disease stages, this defensive response is altered due to a combination of compromised glucose counter-regulation and unawareness of hypoglycaemia, which leads to a pathological mechanism called hypoglycaemia-associated autonomic failure (HAAF) (78).

In HAAF, a cascade of derangements is induced, which increases the likelihood of hypoglycaemic events by lowering the glycaemic threshold at which the counter-regulatory response comes into play (78). The result is a state of reoccurring hypoglycaemic events in which hypoglycaemia-associated warning symptoms are not adequately experienced. This can lead to a vicious circle in which hypoglycaemia, potentially caused by occasional excess insulin treatment, further induces hypoglycaemia (79) with increased, potentially life-threatening, risk of seizures, coma and death (80,81). The prevention of potentially serious complications is, therefore, crucial to facilitating safe participation in exercise training for T1D patients.

Precautions that can be taken before exercise include fast-acting carbohydrate supplement intake (82), the implementation of short high-intensity exercise bouts before aerobic exercise (83) and either taking reduced dosages of insulin prior to exercise (84) or adjusted basal insulin application in the case of insulin pump therapy (85). Overall, management before, during, and after exercise is complex and done to reduce the possibility of entering hypoglycaemic or hyperglycaemic ranges (86). Although it requires frequent capillary glucose evaluation (86), these measurements could also lead to exaggerated compensation and potentially cause hyperglycaemia (87).

1.6 Assessing the condition of the vasculature

1.6.1 Maximum cardiopulmonary exercise testing

Cardiopulmonary exercise (CPX) testing can provide valuable diagnostic data on how the cardiopulmonary, vascular and musculoskeletal systems react to physical strain (88). The integrated function of these systems is representative of the body's condition and function (89). Performing maximum cardiopulmonary exercise (mCPX) testing reflects the peak performance of external and internal respiration and challenges the body's ability to supply, transport and utilise oxygen (88). mCPX is commonly used to determine cardiorespiratory fitness (CRF) (90) by reaching the point of the highest possible provision of energy and provoking complete exhaustion via an incremental exercise protocol. CRF is predictive of all-cause, CVD and cancer mortality (91), and its assessment can aid in risk stratification and the development of therapeutic concepts (91). Peak cardiopulmonary performance is represented by VO_{2max}, which reflects the maximum volume of oxygen the body can transport and utilise at peak exercise and is expressed in millilitres of O2 per kg of body weight per minute [$mL*kg^{-1}*min^{-1}$] (92).

1.6.2 Carotid-femoral pulse wave velocity (cfPWV)

As the most simple, non-invasive, robust and reproducible method to measure arterial stiffness, Pulse wave velocity (PWV) is considered to be the gold standard in determining and quantifying arterial stiffness (93). The stiffening of otherwise elastic proximal arteries, most importantly the aorta and its first branches, is seen as a result of ageing that progressively manifests over time (94). It is a major factor in the rise in systolic and pulse pressure during senescence (95) and one of the first detectable manifestations of altered vessel structure and function (96).

Aortic stiffness measured through PWV can be used as a surrogate marker for cardiovascular events and as an independent predictor of all-cause mortality, especially in subjects with a high baseline cardiovascular risk, such as patients with diabetes (95,97). It is a risk factor in the development of hypertension, coronary artery disease and stroke (98–100) and, therefore, plays a decisive role in the determination of life expectancy (101). Subjects with T1D have significantly increased PWV compared to people in control groups, even when no clinical signs of atherosclerosis are present (26,102). This is especially relevant if they are unable to meet the recommendations of the American Diabetes Association and International Society for Paediatric and Adolescent Diabetes on HbA_{1C}, blood pressure, lipids and BMI (103).

Regular PA has shown to be an effective means of preventing and/or reversing the stiffening of arteries without the use of pharmaceuticals (104). Also, a single unit of exercise can transiently have a positive influence on one’s state of vasculature. After high-intensity interval training, a transitory decrease in PWV and central blood pressure (105) and sustained arterial compliance during the recovery period of up to 24 hours (106,107) can be observed in healthy adults. In contrast, when cardiovascular risk factors like hypertension and obesity are present, high-intensity exercise is immediately followed by an increase in PWV (108,109) which could lead to an aggravation of cardiovascular risk (110). This brings up the question of how high-intensity interval training, as is accomplished during mCPX, alters arterial stiffness during exercise and in the recovery phase among people with T1D.

1.6.3 Retinal vessel calibres

Retinal vessels can be viewed as an easily accessible window into the human microcirculation condition. They measure 100 to 300 µm in size and share comparable anatomy and physiology with vessels of other end organs like the brain and kidneys (111). An elegant way to assess the condition of the retinal vessels noninvasively and quickly and to quantify microvascular impairment is static retinal vessel analysis (SVA). In SVA, photographs from the retinal fundus are used to determine central retinal arteriolar (CRAE) and venular (CRVE) diameter equivalents, which are then used to calculate the arteriolar-to-venular diameter ratio (AVR).

The parameters assessed in SVA are valuable for cardiovascular risk stratification and have predictive value concerning cardiovascular outcomes (112). Low AVRs consisting of narrow CRAE and wide CRVE are associated with various CVDs like stroke (113) and coronary heart disease (114) and elevated cardiovascular mortality (115). Among people with T1D, a low AVR is associated with cardiovascular risk factors (116), and a narrow CRAE is associated with microvascular and macrovascular complications (117). People under high cardiovascular risk frequently show signs of impaired retinal microvasculature like wide retinal venules or narrow retinal arterioles (118). High CRF positively affects retinal vessel diameter (119) and has recently been described to be associated with high AVRs and narrow CRVE values (120). In individuals with T1D, narrow CRAE is associated with sedentary behaviour and wide CRVE is related to low levels of PA (121). In cardiac patients with impaired myocardial perfusion, CRAE and CRVE are narrowed directly after performing mCPX compared to pre-exercise values while they are widened in healthy controls (122). This response can be positively influenced by performing regular PA (122).

1.6.4 Asymmetric dimethylarginine (ADMA)

ADMA is an asymmetrically methylated arginine residue that acts as an endogenous competitive inhibitor of nitric oxide synthase (NOS). NOS is a constitutive endothelial enzyme that produces nitric oxide (NO) from L-arginine. NO acts as an important anti-atherosclerotic molecule by having a vasodilatory effect, inhibiting platelet aggregation (123), modulating endothelial adhesion of leukocytes and monocytes (124), decreasing proliferation of smooth intimal muscle cells (125) and suppressing LDL oxidation (126). Elevated plasmatic concentrations of ADMA lead to decreased NO production and endothelial dysfunction (127) and are present in patients with diabetic retinopathy (128), nephropathy (129) and neuropathy (130). The ADMA-induced endothelial dysfunction is linked to these diabetes-associated microvascular complications (131), and even early, asymptomatic chronic microvascular disease comes with elevated ADMA levels (132).

In conclusion, ADMA plays a major role in the pathogenesis of atherosclerosis by inhibiting NO production and, thereby, leading to endothelial dysfunction and microvascular disease (133). ADMA levels are associated with cardiovascular events and outcomes (134) and are an established marker of cardiovascular risk and disease (135,136). The downregulation of ADMA expression and increased NO production may be central features of improved microvascular function due to exercise (119).

1.6.5 Interleukin-6 (IL-6)

In acute response to exercise, plasmatic concentrations of IL-6 have consistently been reported to be elevated, even more than other cytokines (137,138). IL-6 is released through the contraction of muscles during activity (139), and depending on the intensity and duration of the physical strain, muscle-derived IL-6 rises up to 100-fold during exercise (140,141). Plasmatic levels of IL-6 were identified to be associated with cardiovascular events (142,143) and predict both all-cause and cardiovascular mortality in individuals with pre-existing CVD (144). Traditionally, IL-6 is, therefore, classified as a pro-inflammatory cytokine. However, it is involved in complex immunological and metabolic responses to high-intensity exercise (140), and research has shown that it could also play a role in the anti-inflammatory effect of exercise (138) through the downregulation of inflammatory cytokine production (145,146). Considering its role as a myokine, IL-6 seems to play a favourable role in glucose homeostasis and lipid metabolism (147), and it was found to have positive effects on glucagon and insulin secretion by influencing the production, release, and beta-cell signalling of Glucagon-like peptide-1 (GLP-1) (148,149) while also regulating insulin excretion by directly affecting pancreatic beta cells independently of GLP-1, both in vitro and in vivo (150,151). Furthermore, it induces lipolysis and fat oxidation (152) and plays a role in the browning of adipocytes (153).

Because IL-6 is run associated with CVD and mortality in the long but induces temporary metabolic benefits following PA, it could be classified as an inflammation-responsive cytokine (138) that reaches its plasmatic peak directly after exercise and then quickly drops back to pre-exercise values in the hours following exercise (154). Long-term adaption to exercise involves a reduction of IL-6 production and results in lower basal and exercise-response IL-6 concentrations (140). Among subjects with T1D, monocytic IL-6 is significantly elevated at rest compared to that in healthy controls, so it can be seen as a marker of inflammation (155). Increased baseline levels of IL-6 are also present in patients with diabetic retinal microvascular complications (156).

1.6.6 N-terminal pro-B-type natriuretic peptide (NT-proBNP)

B-type natriuretic peptide (BNP) is a biologically active part of the natriuretic peptide family that is primarily secreted from ventricular cardiac tissue (157). Its secretion is dependent on cardiac volume and pressure load, and it plays an important role in decreasing blood pressure and regulating the body's fluid volume (157,158) by stimulating sodium extraction and diuresis, inducing vascular permeability and vasodilation and inhibiting sympathetic activity and the renin–angiotensin–aldosterone system (157). This regulation, in combination with antifibrotic and lusitropic, effects make BNP a cardioprotective and vasoprotective hormone that is expressed in reaction to myocyte stretching (157). Molecular fragments of its precursor (NT-proBNP) are secreted in equimolar concentrations but are not biologically active and are passively cleared from the body (159). Therefore, NT-pro BNP has a longer half-life than BNP and, consequentially, higher blood concentration (159) making it easier to detect. Because of this reactionary expression to cardiac overload and neurohumoral stimulation, BNP and NT-proBNP are established biomarkers for heart disease detection and severity evaluation (160,161). NT-proBNP is, therefore, presumably more sensitive in early heart failure detection because of its longer biological half-life (162).

In people with T1D, plasmatic BNP is elevated compared to those of non-diabetic controls, most notably in individuals with high HbA_{1C}, systemic hypertension or microalbuminuria (163). NT-proBNP has been described as a reliable marker for asymptomatic cardiac dysfunction among people with diabetes that corresponds with myocardial alterations. Elevated NT-proBNP levels can be found at a young age in individuals with T1D (164,165). BNP, and especially NT-pro BNP, can be utilised to detect diastolic dysfunction (164,166), which represents the first phase of diabetic cardiomyopathy (165,167). Research has shown that there is an inverse correlation between BNP release and VO_{2max} in healthy individuals (168,169). Among healthy people, after strenuous endurance performances, an increase in BNP and NT-proBNP has consistently been reported and could be indicative of impaired right ventricular function and elevated pulmonary pressure (170,171). It was shown that NT-pro BNP is strongly related to CRF in patients with heart failure (172), and the implementation of repeated PA has been shown to lower BNP and NT-pro BNP concentrations among heart failure patients (173).

1.6.7 Aim of the thesis

The parameters selected for this thesis all represent the human vasculature ranging from micro- to macrovasculature. As described above, they have all shown to react promptly to PA and are known risk predictors for CVD and CV mortality in T1D. Because it remains uncertain if, and how the compromised autonomic vascular response, that can be found in T1D (55), alters the hemodynamic response, we explored the immediate effects of PA on the impaired vasculature of people with T1D. Thereby we aimed to increase the understanding of the prophylactic capability of high-intensity exercise in T1D, which has shown to be able to prevent micro- and macrovascular complications in T2D (174). Furthermore, we wanted to improve the understanding of the physiological processes during and after a high-intensity exercise bout in T1D.

Another important aspect for us was to explore the relationship between diabetic disease characteristics and the investigated parameters. Of interest for us was, to gain a better understanding on how, and to what extent, these characteristics, that are all important in the clinical disease evaluation of people with T1D, influence vascular exercise responsiveness and health.

Regarding the existing uncertainty about how and to what extent, regular exercise can alter the vasculature in T1D patients, we aimed to analyse the effect of cardiorespiratory fitness CRF on microvascular and macrovascular alterations. This was achieved by analysing a set of preselected cardiovascular biomarkers and comparing them to CRF of the study participants.

2 Methods

2.1 Trial design

This trial is embedded in the larger ULTRAFLEXI 1 (UF-1) study, which is a prospective single-center trial in participants with T1D at the Medical University of Graz. All testing relevant to this thesis was done on two consecutive screening days for this study.

In this thesis, we aimed to quantify the response of the vasculature to maximum CPX testing in patients with T1D. This objective is achieved via an interventional trial by prospectively measuring and later analysing if, and in which quantity PWV, NT-proBNP, IL-6, ADMA, AVR, CRAE, and CRVE are affected by CPX testing and how they correlate with diabetic disease characteristics in people with T1D at five different testing time points.

The parameters were selected to represent the condition of the subjects‘ vasculature and assessed immediately before (T0), immediately after (T1), 30 min after (T2), 60 min after (T3), and for NT-proBNP and IL-6, 24h after (T4) the CPX testing both invasively and non-invasively.

Therefore, it was possible to compare the pre- to post-exercise response and to analyse the development of exercise effects over time. The CPX-testing was performed on the first day of screening and the data was acquired in both visits on consecutive days.

At the time points, PWV measurements and retinal imaging were conducted by a trained researcher and a venous sample was collected for the assessment of IL-6, NT-proBNP, and ADMA. The blood samples were then centrifuged, and serum was pipetted and frozen until further analysis.

At the first screening day, the participants diabetes treatment history was assessed, including their daily insulin dose and the duration of diabetes. Additionally, blood samples were drawn for laboratory examination of HbA_{1C} and C-peptide.

2.2 Trial population

A total of five male and five female participants with type 1 diabetes were enrolled for the thesis and study between May and November 2020. All the participants were recruited from a pool of people who previously expressed their consent to participate in clinical research at the diabetic outpatient clinic of the University Hospital of the Medical University Graz.

As the participants for the trial were preselected for the larger interventional UF-1 study, its inclusion and exclusion criteria also apply here. These criteria were selected carefully to acquire a homogenous study population and to prevent bias from external factors and are listed below.

Included individuals had to meet the following criteria.

1. Between 18 to 65 years (both inclusive) of age
2. Have a body mass index between 18.0 and 29.9 kg/m^2 (both inclusive).
3. Clinically diagnosed T1D $\geq$ 12 months
4. T1D in a stable state (HbA$_{1C}$ $\leq$ 10% (86 mmol/mol))
5. T1D treated with multiple daily insulin injections $\geq$ 12 months.
6. Be physically active, performing regular physical cardiorespiratory activity over the last 3 months prior to screening.
7. Mass-specific peak oxygen consumption (VO$_{2max}$) >20 mL/kg/min.

Participants were excluded from the exercise visit or scheduled to another exercise day if any of the following applied.

1. Known or suspected hypersensitivity to trial product(s) or related products
2. Receipt of any investigational medicinal product within 1 month prior to screening in this trial
3. Haemoglobin >13.0 g/dl (male) or > 12 g/dl (female)
4. Systemic (oral or i.v.) corticosteroids, monoamine oxidase (MAO) inhibitors, non-selective beta-blockers, growth hormone, non-routine vitamins, and herbal products. Furthermore, thyroid hormones are not allowed unless the use of these has been stable during the past 3 months.
5. Suffer from or history of a life-threatening disease (i.e. cancer judged not to be in full remission except basal cell skin cancer or squamous cell skin cancer), or clinically severe diseases that directly influence the study results, as judged by the investigator. This does not prohibit the participation of patients taking medications that influences the metabolism (e.g. statin) or cardiorespiratory system (e.g. asthma spray) as long as the therapy is stable and is not adapted throughout the run of the trial. Furthermore, it does not exclude patients who have celiac disease (or similar diseases or allergies), if the disease is stable, and patients are able to stay on their specific (e.g.) gluten-free diet.
6. Participant with a heart rate < 35 beats per minute (bpm) at screening (after resting for 5 min in supine position)

7. Cardiac problems defined as decompensated heart failure (New York Heart Association (NYHA) class III and IV) 10 at any time and/or angina pectoris within the last 12 months and/or acute myocardial infarction at any time.
8. Supine blood pressure at screening (after resting for 5 min in supine position) outside the range of 90-150 mmHg for systolic or 50-95 mmHg for diastolic (excluding white-coat hypertension; therefore, if a repeated measurement on a second screening visit shows values within the range, the participant can be included in the trial). This exclusion criterion also pertains to participants being on anti-hypertensives.
9. Clinically significant abnormal ECG at screening, as judged by the investigator.
10. Severe retinopathy or maculopathy and/or severe neuropathy, in particular autonomic neuropathy, as judged by the investigator.
11. Any chronic disorder or severe disease which, in the opinion of the investigator might jeopardise participants' safety or compliance with the protocol.
12. History of multiple and/or severe allergies to drugs or foods or a history of severe anaphylactic reaction.
13. Significant history of alcoholism or drug/chemical abuse as per investigator's judgement or a positive result in the urine drug/alcohol screen at the screening visit.
14. Smoker (defined as a participant who is smoking more than 5 cigarettes or the equivalent per day)
15. Not able or willing to refrain from smoking or use of nicotine substitute products during the inpatient period.
16. Recurrent severe hypoglycaemia (more than 1 severe hypoglycaemic event during the past 12 months).
17. Hypoglycaemic unawareness as judged by the investigator or hospitalisation for diabetic ketoacidosis during the previous 12 months.
18. Participant with mental incapacity or language barriers precluding adequate understanding or cooperation or who, in the opinion of their general practitioner or the investigator, should not participate in the trial.
19. Potentially non-compliant or uncooperative during the trial, as judged by the investigator.
20. Any condition that would interfere with trial participation or evaluation of results, as judged by the investigator.

21. Female of childbearing potential who is pregnant, breastfeeding or intend to become pregnant, or is not using adequate contraceptive methods (adequate contraceptive measures include sterilisation, hormonal intrauterine devices, oral contraceptives, sexual abstinence, or vasectomised partner).
22. Using a real-time CGM device, which allows to individually set glycaemic thresholds (e.g. Dexcom G4/5/6, Medtronic Guardian, or FreeStyle Libre 2 systems). That does not exclude using Freestyle Libre 1
23. Renal function eGFR (CKD-EPI) < 50 mL/min/1.73 m^2.

Written informed consent was obtained of all subjects before entering the study, which was conducted according to the principles of the declaration of Helsinki. Withdrawal from the trial was possible at all times and for any reason. The study was approved by the ethics committee of the Medical University of Graz.

2.3 Maximum cardiopulmonary exercise (CPX) testing

At the first visit, subjects performed a maximal exercise test, on a stationary cycle ergometer (Ergoselect 4, Ergoline, Suessmed, Austria) in a comfortable and quiet environment with a room temperature of 20 to 22°C. Before the exercise, participants were asked to sit quietly for a three-minute resting period and then to complete a three-minute 20 W warmup. During exercise, the starting workload of 20W was incrementally increased every 60 seconds by a 10 W, 15 W, or 20W protocol until volitional exhaustion.
This protocol was predefined by an experienced exercise physiologist and individually adjusted for level of fitness, age, and gender to achieve a fatigue-limited duration of exercise between 8 to 12 minutes. After finishing mCPX, participants underwent a three-minute active (20 W) cool down and a three-minute passive recovery period (0W).
Ventilatory gas exchange measurements (MetaMax 3b, Cortex, Germany) were performed to determine VO_{2max}. Immediately before each test, the sensors of the system were calibrated.
During the exercise testing, heart rate was measured via chest belt telemetry (s810i, Polar Electro, Espoo, Finland). For safety measures, cardiovascular monitoring was conducted via 3-lead electrocardiogram and intermittent manual blood pressure measurements during exercise. Capillary blood glucose was measured taken from the fingertip (FreeStyle Libre, Abbott, UK) and the earlobe minutely (Biosen C-Line, EKF Diagnostics, UK). Blood

lactate concentration was measured every minute from blood samples which were taken from the earlobe (Biosen C-Line, EKF Diagnostics, UK).

2.4 PWV

PWV was measured via the carotid-femoral method (cfPWV) using the Vicorder-System (Vicorder, SMT Medical, Wuerzburg, Germany) fitted with one 30-mm-wide and one 100-mm-wide inflatable cuff.

For this method, one cuff is fixed around the neck so that the probe lies above the carotid artery, while the second cuff is fixed as high as possible around the root of the right thigh to measure the femoral pulse. The distance between the suprasternal notch and the centre of the thigh cuff is then measured superficially to estimate the distance (d) between the cuffs. Subsequently, the cuffs are inflated automatically to 65 mmHg and the oscillometric signal from both inflated cuffs is processed by a built-in algorithm and depicted as two individual pressure waves. The transit time of the pulse wave is automatically calculated using the time delay between the arrival of the pressure wave at the carotid cuff and the femoral cuff.

The velocity with which the pulse wave travels through the aorta is then computed by putting d over transit time ratio [m/s].

2.5 Retinal imaging

For the retinal screening, the CR-2 non-mydriatic digital retinal Canon camera (CR-2 AF; Canon, Tokyo, Japan) was used for an alternative non-invasive retinal vessels' assessment. fundus photographs were taken in a shaded room from the right eye at a 5-degree angle from the nasal side of the macula with a capturing angle of 45 degrees.

Retinal images were stored on a laptop and the retinal image of highest quality, centred on the participants' optic disc was selected by a trained grader. The grader performed vessel measurements on the optic discentered image of the right eye. The largest six arterioles and venules coursing through a zone between 0.5 and 1 disc diameter from the optic disc margin were measured. Estimates were summarized as CRAE and CRVE, representing the average diameter of arterioles and venules of the eye, respectively. This analysis was done using the semi-automated iFlexis Software (Vito, Belgium).

2.6 ADMA

The blood samples were centrifuged immediately after they were taken, and the proportioned plasma was stored at -80°C until further analysis.

Serum-ADMA was measured via competitive Enzyme-Linked Immunosorbent Assay (ADMA ELISA K 7828, Immundiagnostik AG, Bensheim Germany).

2.7 IL-6 and NT-proBNP

IL-6 and NT-proBNP plasma concentrations were determined using an automated electro-chemiluminescence immunoassay (ECLIA; Elecsys, Roche Diagnostics, Switzerland) using the Roche Elecsys 2010 Immunoassay Analyzer (Roche Diagnostics, Switzerland).

2.8 *Telomerase activity*

Initially, we planned to include Telomerase activity as one of our vascular parameters and the blood samples collected to determine telomerase activity were centrifuged directly after mCPX and stored for further analysis. Unfortunately, the laboratory that was responsible for the analysis of this parameter was overworked with performing PCR during the ongoing Covid-19 crisis and could not finish the analysation in time. Therefore, the parameter could not be utilized for this thesis.

2.9 Statistical methods

Statistical analyses were performed using GraphPad Prism (version 8.0, San Diego, USA). All calculations were reassessed for normal distribution with Shapiro-Wilk normality-test. Before exploring the differences between the timepoints, normality-testing was performed. If more than half of the data sets passed the test for normal distribution, one-way analysis of variance (ANOVA) with Tukey's multiple comparisons test was performed to depict and verify differences between the baseline and post-mCPX elicitations. If less than half of the data sets passed the test for normal distribution, nonparametric Friedmann-test with Dunn's multiple comparisons test was used.
For better comparison between the parameters, the data was normalized using z-transformation ($Z = (X-\mu)/\sigma$) and then converted to the same scale where T0 = 0.00. The scale conversion of each parameter was done by calculating the difference between each individual normalized value and its correspondent normalized value at T0.

The association between VO_{2max} and the parameters was explored by performing linear regression analysis. This was done by modelling a best-fit slope for the acquired values at each timepoint as well as for the delta between adjacent timepoints.

To explore the relation between the subject's characteristics and the acquired vasculature-markers, participants were grouped by acquired markers, namely diabetes duration, daily dose of insulin per kilogram of body weight (TDD/kg), HbA_{1C}, C-peptide, age, BMI, and sex. Grouping by diabetes duration, age, and TDD/kg was done by calculating the median and then using it as a cut-off value to distribute the participants into two groups. Participants were grouped by HbA_{1C}, using the common cut-off value of 7.0 %, grouped by BMI using the cut-off value of 24.9 kg/m^2, grouped by sex into male and female and grouped by C-peptide whether a detectable C-peptide concentration was present or not. Differences between the groups were the explored using multiple t-tests and statistical significance was corrected using the Holm-Sidak method. For all tests, a $p\text{-value} < 0.05$ was considered statistically significant.

2.10 Study approval

This thesis and the underlying trial study were approved by the ethics committee of the Medical University of Graz, Austria (registry number: IRB00002556). Participant's written informed consent was obtained before any trial-related activities. This trial was performed according to Good Clinical Practice and the Declaration of Helsinki.

3 Results

All ten subjects were able to participate in mCPX and all following investigations on both testing days. Unfortunately, eight of the retinal photographs taken after CPX were insufficient for the assessment as judged by the trained grader. Therefore, CRAE, CRVE both had the anticipated ten results at T0, but only nine at T1, eight at T2, and five at T3. Subsequently, AVR was only calculatable for these values.

As shown, the Data was able to demonstrate a distinct reaction of the vasculature following PA (Fig. 1 and 2).

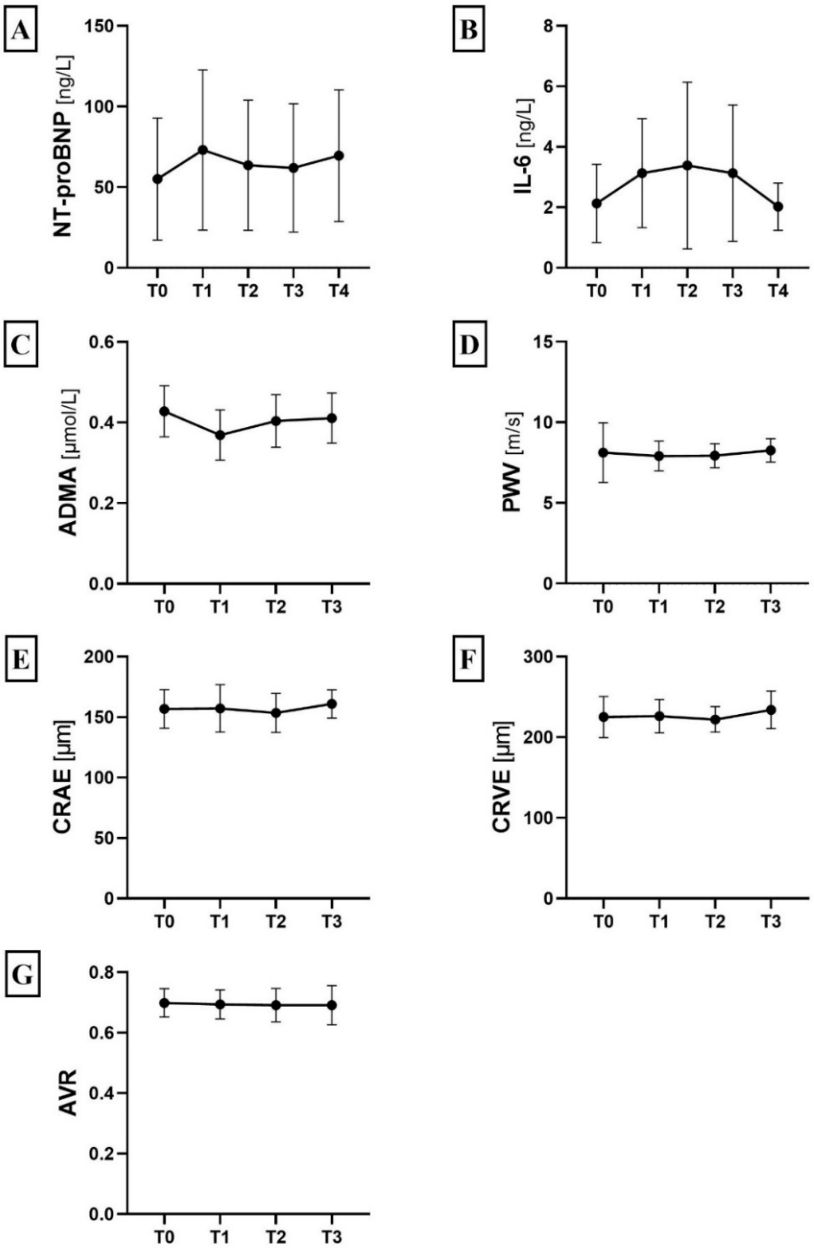

Figure 1. Mean values of NT-proBNP (A), IL-6 (B), ADMA (C), PWV (D), CRAE (E), CRVE (F), and AVR (G) at baseline (T0) and at 0 min (T1), 30 min (T2), 60 min (T3), and, if applicable, at 24 h (T4) after mCPX. Values are means ± SD.

A comparison between the parameters was enabled by z-transforming and scale-converting the parameter's values, which can be seen in Figure 2. The significant answer of NT-proBNP, ADMA, and IL-6 to the high-intensity strain could thereby be visualized (Fig. 2).

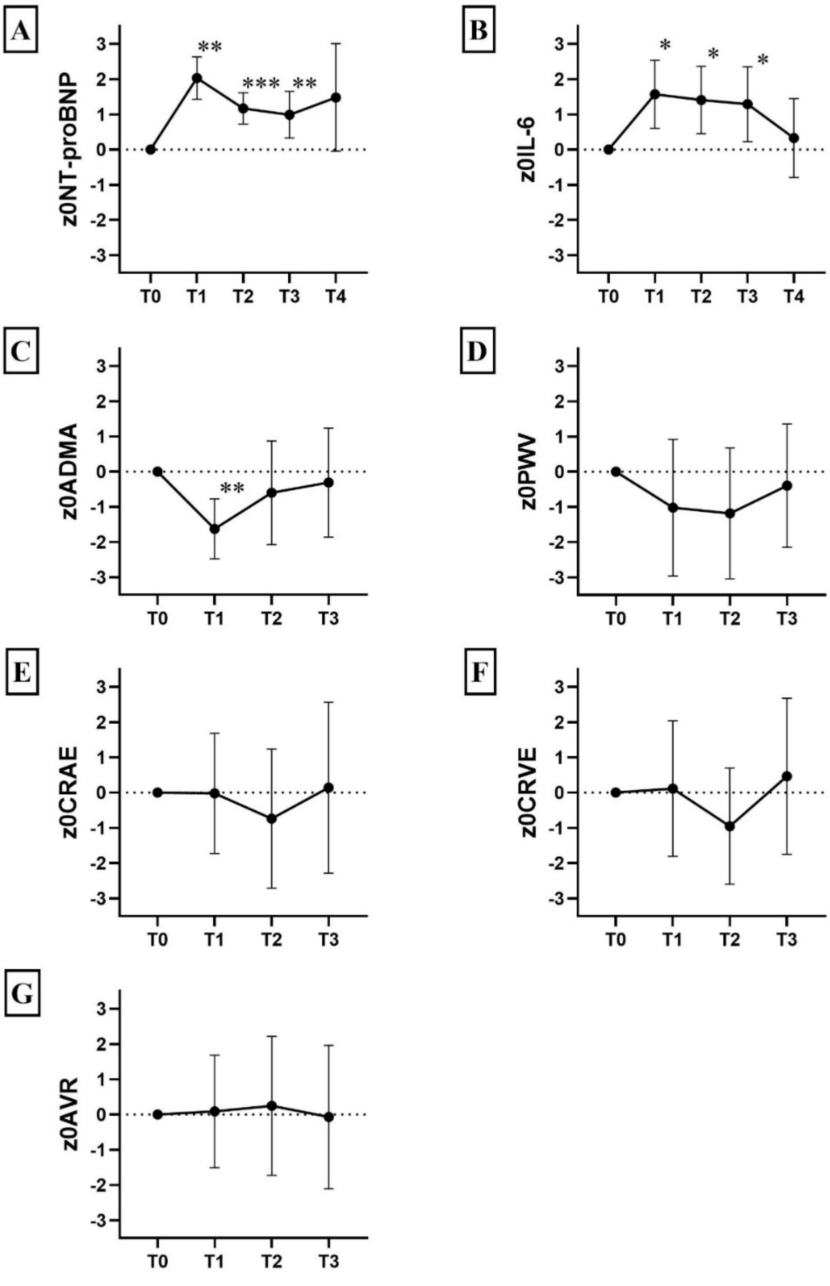

Figure 2. Mean values of z0NT-proBNP (A), z0IL-6 (B), z0ADMA (C), z0PWV (D), z0CRAE (E), z0CRVE (F), and z0AVR (G) at baseline (T0) and at 0 min (T1), 30 min (T2), 60 min (T3), and, if applicable, at 24 h (T4) after mCPX. Values are means ± SD
Significantly different from T0: *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$

In the parameters determined from blood samples, a notable pre- to post exercise impact was confirmed. These parameters, namely IL-6 ($p = 0.023$), ADMA ($p = 0.011$) and NT-proBNP ($p = 0,010$), all changed significantly from T0 to T1 (Table 1).

After the initial effect, NT-proBNP- and IL-6- concentrations remained elevated during the hour following mCPX as they were significantly increased when comparing T0 to T2 ($p < 0.0001$ and $p = 0.0015$) and T0 to T3 ($p = 0.008$ and $p = 0.044$), representing an ongoing reaction to the mCPX-stimulus (Table 1).

24 hours after mCPX, IL-6 and NT-proBNP had returned to pre-exercise values and there was no significant difference between T0 and T4 (Table 3). It is worth mentioning though that the comparison of NT-proBNP values between T0 and T4 was of borderline statistical significance ($p = 0.088$) (Table 1).

After their initial considerable decrease, ADMA levels quickly relapsed to values similar to baseline and there was no significant difference between neither T0 and T2 nor T0 and T3 (Table 1).

There was no significant difference between PWV-values at baseline (T0) and the three post-CPX time points (T1- to T3). Subject’s arterial stiffness was unaffected ($p > 0.05$) by the stimulus during the investigational period (Table 1).

Similar results were acquired for the data collected in SVA. AVR, CRAE, and CRVE were not significantly ($p > 0.05$) influenced by mCPX, and all had very similar values pre- to post mCPX, and the mixed effects analysis did not show significant differences between T0 and the time points T1 to T3 (Table 1).

Table 1. Results of the multiple comparisons testing between the timepoints (T1-T4) and baseline (T0).

	T0 vs T1	T0 vs T2	T0 vs T3	T0 vs T4
IL-6	(p = 0.023) * MD = 1.00 ± 0.61	(p = 0.015) * MD = 1.23 ± 1.43	(p = 0.044) * MD = 1.00 ±0.95	(p > 0.999) MD = -0.11 ± 1.56
NT-proBNP	(p = 0.005) ** MD = 17.96 ± 12.14	(p < 0.001) *** MD = 8.65 ± 4.01	(p = 0.004) ** MD = 6.88 ± 4.42	(p = 0.088) MD = 14.40 ± 17.06
ADMA	(p = 0.006) ** MD = -0.059 ± 0.043	(p = 0.465) MD = -0.024 ± 0.056	(p = 0.766) MD = -0.017 ± 0.064	n/a
PWV	(p = 0.97) MD = -0.21 ± 1.78	(p = 0.976) MD = -0.19 ± 1.74	(p = 0.988) MD = 0.14 ± 1.65	n/a
CRAE	(p > 0.999) MD = -1.053 ± 10.27	(p = 0.823) MD = -3.929 ± 10.9	(p = 0.884) MD = -0.168 ± 12.48	n/a
CRVE	(p = 0.884) MD = -3.187 ± 17.65	(p = 0.830) MD = -7.128 ± 14.8	(p = 0.809) MD = -0.674 ± 21.0	n/a
AVR	(p= 0.959) MD = -0.003 ± 0.028	(p = 0.890) MD = 0.003 ± 0.027	(p = 0.977) MD = 0.005 ± 0.043	n/a

Expressed are the adjusted p-value of the comparisons test with the mean difference (MD) ± standard deviation (SD) between each test point.
*: p ≤ 0.05; **: p ≤ 0.01; ***: p ≤ 0.001

The biggest relative mean difference between T0 and T1 was seen in z0NT-proBNP (MD = 2.03 ± 0.58), followed by z0ADMA (MD = -1.63 ± 0.81), z0IL-6 (MD = 1.57 ± 0.92), z0PWV (MD = -1.02 ± 1.84) (Fig. 3). The retinal vessel calibres comparatively underwent the smallest changes from pre- to post mCPX as the relative mean differences between T0 and T1 of z0CRVE (MD = 0.12 ± 1.81), z0CRAE (MD = -0.02 ± 1.52) and the resulting z0AVR (MD = 0.09 ± 1.50) was clearly smaller than for the other parameters (Fig. 3).

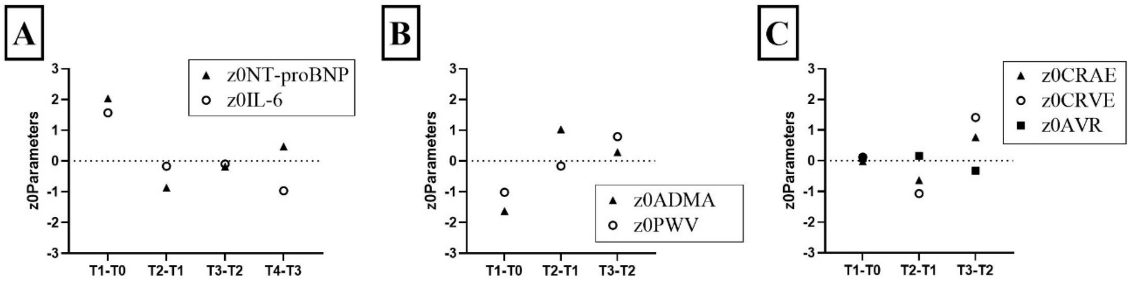

Figure 3. Z-transformed and scale-converted (z0) NT-proBNP and IL-6 (A), ADMA and PWV (B) and CRAE, CRVE and AVR (C) relative mean difference between adjacent timepoints.

The linear regression analysis did not show a significant ($p > 0.05$) correlation between VO_{2max} and any of the investigated parameters at the timepoints.

For NT-proBNP, IL-6, PWV and the retinal vessel calibres, there was no significant ($p > 0.05$) correlation between VO_{2max} and the delta of adjacent timepoints.

However, there was a significant ($p_{(two\ tailed)} = 0.0092$; $r^2=0.59$) inverse correlation betweenVO$_{2max}$ and change of ADMA concentrations from T0 to T1 indicating that individuals with higher VO_{2max} had a bigger decrease in ADMA concentration from pre- to post mCPX (Fig. 4).

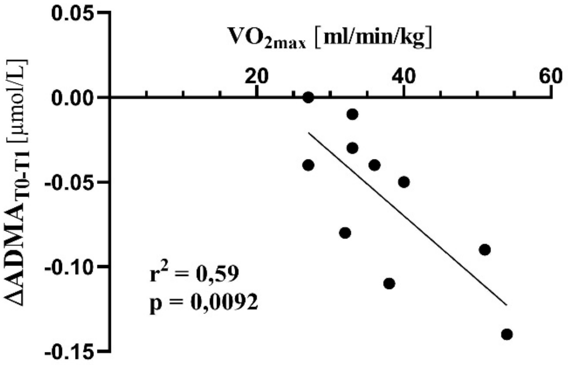

Figure 4. Linear regression model for VO_{2max} vs. ΔADMAT0-T1. Expressed are the significant deviation from zero (p) and the goodness of fit (r^2) of the slope; n = 10

The CPX-testing revealed a mean VO_{2max} of the subjects of 37.10 ±8.68 ml/min/kg with a mean peak workload of 214.50 ± 60.85 W (Table 2).

Due to the procedure of incrementally exercising until maximum exhaustion, exercise duration of mCPX (tCPX) can slightly differ between each subject (Table 2). To keep these differences as small as possible, different exercise protocols were implemented as described above. The mean duration of mCPX was 13:35 ±02:57 min.

Table 2. Results of the mCPX-testing

VO_{2max} (mL/min/kg)	P_{max} (W)	Peak aerobic power ($W \cdot kg^{-1}$)	Duration of mCPX (min)	mean La (mmol/L)	mean Glc (mg/dL)
37.10 ± 8.68	214.50 ± 60.85	2.75 ± 0.70	13:35 ± 02:57	3.84 ± 0.98	178.89 ± 31.97

Values are given as mean ± SD.

When reassessed, there was a significant correlation between tCPX and AVR at T3 ($p = 0.032$; $r^2 = 0.82$) and between mean glucose concentrations and AVR at T3 ($p = 0.047$; $r^2 =$

0.78) (Fig. 5). In this context, it is important to mention that the AVR-values at T3 consisted only of data from five participants, because of incomplete data as mentioned above.

The other parameters did not correlate significantly ($p > 0.05$) with the duration of mCPX or mean glucose concentrations at any of the time points.

Lactate concentrations during mCPX did not significantly ($p > 0.05$) correlate with the parameters at any of the timepoints.

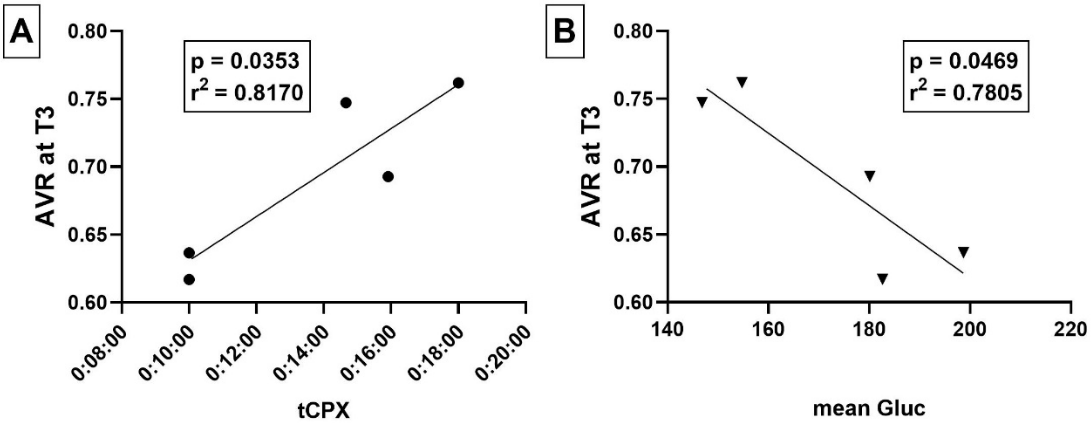

Figure 5. Graphical results of the linear regression analysis between AVR at T3 and tCPX (A), and AVR at T3 and mean glucose during mCPX (B). Expressed are the significant deviation from zero (p) and the goodness of fit (r^2) of the slope; $n = 5$.

The study participants were grouped by diabetes duration, age, HbA_{1C}, C-peptide, TDD/kg, and BMI (Table 3). For the Grouping by diabetes duration (MED = 22.5 years), TDD/kg (MED = 0.49 U/kg) and age (MED = 43 years the median), the median was used, respectively (Table 3).

For the grouping by C-peptide (Mean = 0.104 pmol/L) participants were differentiated whether relevant plasma concentrations were detectable ($n_{C\text{-peptide} > 0.00} = 5$), or not ($n_{C\text{-peptide} = 0.00} = 5$). For the grouping by HbA_{1C} (Mean = 7.42 %), the cut-off value of 7.0 % was used ($n_{HbA1C \leq 7.0} = 2$; $n_{HbA1C > 7.0} = 8$). For the grouping by BMI, participants were divided whether they were normal weight ($BMI \leq 24.9$) or overweight ($BMI > 24.9$). Additionally, participants were grouped by sex ($n_{male} = 5$; $n_{female} = 5$).

Table 3. Subjects' characteristics relevant for grouping.

Age (years)	**Height (m)**	**Weight (kg)**	**BMI (kg.m^{-2})**
42.8 ± 9,79	1.78 ± 0.11	78.7 ± 16.6	24.53 ± 2.63
TDD/kg [U/kg]	**HbA1C [%]**	**TDD [years]**	**C-peptide [pmol/l]**
0.51 ± 0.20	7.42 ± 0.65	21.4 ± 8.4	0.104 ± 0.22

Values are given as mean ± SD

The grouped analysis of the parameters showed a significant difference (adjusted p-value = 0.020) between the PWV of the group with detectable C-peptide (C-peptide > 0.00) and the group that had no detectable C-peptide secretion (C-peptide = 0.00) at baseline (Fig. 6). Furthermore, a significant difference (adjusted p value = 0.030) between the NT-proBNP values of the C-peptide groups at T1 was found (Fig. 6).

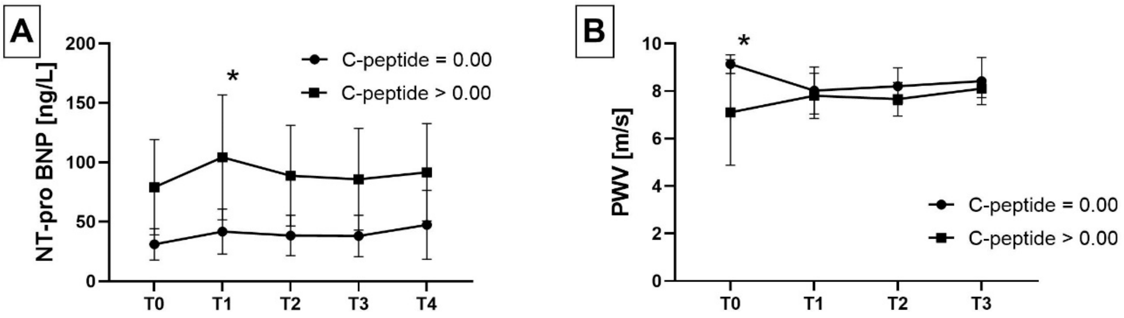

Figure 6 NT-proBNP (A) and PWV (B) at the timepoints, grouped by detectable (C-peptide > 0.00) and non-detectable (C-peptide = 0.00) C-peptide secretion. Values are means ± SD; T-test: *: p ≤ 0.05

The grouping by sex revealed a significantly (adjusted p-value = 0.00006) elevated IL-6 concentration in females at baseline (Fig. 7).

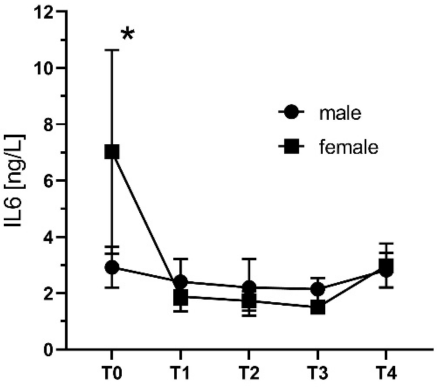

Figure 7. IL-6 at the timepoints, grouped by sex. Values are means ± SD; n=10; T-test: *: p ≤ 0.05

The grouping by diabetes duration ($p > 0.05$), TDD/kg ($p > 0.05$), HbA_{1C} ($p > 0.05$), BMI ($p > 0.05$) and age ($p > 0.05$) did not show significant differences.

4 Discussion

By collecting and analysing data of selected parameters that represent both the micro- and macrovasculature of people with T1D, this thesis helps in the understanding of regulatory mechanisms of the vasculature induced by high-intensity exercise bouts.

The investigation was done in both male and female adult participants with a wide range in age. Subjects reached a VO_{2max} that lies within the range of a well-trained status for people with T1D (174). By looking at each parameter, various clinical conclusions can be drawn from the data as presented in the following paragraphs.

ADMA

The transient decrease in plasma ADMA concentrations can be explained as an immediate response to endothelial shear stress that involves an upregulation of the NO-vasodilatory system. As NO has vasoprotective, anti-sclerotic and anti-thrombotic qualities (123) its upregulation contributes to the beneficial effects of PA.

From the data can be concluded that in people with T1D, even a single bout of PA that is as short and vigorous as mCPX, activates vascular adaptation that contributes to the integrity of the endothelial function and could be beneficial in microvascular disease prevention.

The following fast relapse can be interpreted as a rebound to pre-exercise values suggesting that the initial impact is of temporary character.

The data collected for this trial was not able to confirm an inverse correlation between exercise capacity and resting ADMA concentrations that had been previously reported in subjects with increased cardiovascular risk (175), chronic heart failure (176) or with older age (177). The acquired data goes more in line with a study conducted in healthy individuals that showed no relation between plasma ADMA concentrations and VO_{2max} (178).

The mean difference from pre- to post-mCPX however, was significantly correlated to VO_{2max}. This could imply that individuals with T1D, that have higher CRF profit more from exercise induced ADMA-dependent vasoregulation, which represents a novel insight on the effects of CRF on endothelial function in T1D.

IL-6

Similarly to previous findings in healthy individuals, IL-6 concentration reached its plasmatic peak shortly after exercise (154). They then dropped back to pre-exercise values in the hours following exercise as demonstrated in Figure 1. This is likely due to its elevated release from contracting muscles during mCPX and could play a role in the regulatory effect on inflammation of exercise (138).

Cardiorespiratory fitness was not significantly related to IL-6 levels before or after exercise, which underlines the ambiguous effect of regular exercise in people with T1D.

In many, but not all previously reported findings, women had greater IL-6 concentrations than men (179). In our acquired data, this difference was also significant at baseline. At the post mCPX timepoints however, it was no longer present, indicating different stimulus-reaction in men and women.

NT-proBNP

An increase in NT-proBNP following mCPX was observed. This can be interpreted as an intact reaction to increased ventricular wall stress during exercise in form of a counter regulation to the sympathetic stimulus and activation of the renin–angiotensin–aldosterone system to preserve adequate ventricular filling and prevent a surge in blood pressure (157). Studies showed that BNP release during exercise is inversely related to VO_{2max} in healthy subjects (168,169). The current data was unable to confirm this relation in individuals with T1D as the changes in NT-proBNP concentrations did not correlate with VO_{2max}. This would imply that BNP and NT-proBNP release in response to mCPX is independent of CRF in people with T1D. It will be of interest to investigate if this relation changes after the exercise intervention that is a part of the UF-1 study and will be explored in future publications.

At all timepoints, the mean NT-proBNP concentration of subjects with preserved C-peptide secretion was lower than in those with no detectable C-peptide. This difference was statistically significant at T1, where mean NT-proBNP concentrations of the group with no detectable C-peptide where almost 2.5-fold. This difference in NT-proBNP concentration indicates an improved ventricular function when C-peptide secretion is present in individuals with T1D.

PWV

The obtained PWV-values showed a non-significant decrease after CPX but the interindividual differences were quite substantial as the pre to post exercise difference ranged from -1.6 m/s up to +4.4 m/s. It is possible that these differences are a result of the ambivalent effects of exercise bouts on the vasculature when a risk factor like T1D is present. On the one hand PWV has shown to decrease after PA (105) and subjects benefit from higher arterial compliance up to 24 hours following exercise (106,107). On the other hand, if a person has cardiovascular risk factors, PWV increases after PA (108,109).

In the tested subjects, the absence of a post-exercise decrease of PWV could be an indicator for an altered hemodynamic response following exercise and the mixed results underline the necessity for an individual cost-risk-consideration when practicing exercise training for people with T1D.

There was no significant relationship between CRF and PWV. The authors of a study in subjects with cardiovascular risk factors that found similar results speculated, that in people without diagnosed CVD, there may only be a weak association between the two factors compared to individuals with progressed vascular damage (180).

Subjects with detectable C-peptide blood concentrations showed to have a significantly lower PWV at baseline. This underlines the presence of a beneficial effect of obtained insulin secretion in people with T1D and indicates that it positively affects arterial compliance.

SVA

No significant differences could be detected between baseline and the three post-exercise timepoints for CRAE, CRVE and AVR. This diverges from previous findings that documented a clear impact of endurance testing on CRAE and CRVE (122). A missing response to mCPX could reveal altered microvascular reactivity in T1D.

VO_{2max} did not correlate with the retinal vessel calibres acquired from SVA.

From the available data it can be concluded that the microvasculature of people with T1D may not benefit from CRF as clearly as people with other forms of vascular impairment (122).

Interestingly, AVR at T3 did correlate with the duration of the exercise stimulus and was negatively correlated with mean glucose concentrations during the testing.

This implies that it could be beneficial to emphasize longer training duration rather than high physical impact and to avoid excessive blood glucose to achieve a prolonged microvascular benefit from an exercise unit.

It must be regarded however that not all retinal photographs were sufficient for grading and therefore only five data sets were collected for SVA at T3.

Limitations

This thesis is an excerpt of an ongoing study which is surely the main reason for its limitations. The sample size of only ten participants is subject to increase as more participants will be screened and therefore undergo mCPX and data will be elicited. On top, the lack of a control group takes away from the comparability of the data, which will also be addressed in the study as a healthy control group will also undergo the same examinations. Furthermore, each study-participant will be screened a second time after finishing a multiple-week exercise program with three units of exercise per week. This will enable an individual comparison before and after exercise intervention and contribute to the expressive power of the data.

One cutback was the fact, that Telomerase activity could not be analysed in time to be implemented in the thesis. Further UF-1 study publications will be able to use this interesting parameter and can thereby enable insights into the impact of CRF on cellular senescence.

Conclusion

The results show a clear beneficial effect of mCPX on IL-6, NT-proBNP and ADMA. This underscores the need for implementation of CPX to the daily lives of people with T1D as recommended in the current guidelines to prevent diabetic micro- and macrovascular complications (64). PWV and retinal vessel calibres were not significantly influenced by mCPX which could be a sign of alterations in the hemodynamic response to exercise in people with T1D.

The change of most of the parameters was not associated with CRF, implying that people with T1D benefit from CPX independently of their exercise capacity.

With the positive correlation between VO_{2max} and change in ADMA concentration from pre- to post mCPX values can be shown that individuals with higher CRF have a more pronounced endothelial reaction to high-intensity exercise.

Higher pre-exercise IL-6 in women compared to men and a post exercise alignment of the parameter could be a hint, that female participants profited more from immunomodulatory effects of exercise.

The significant reduction in NT-proBNP and PWV in the Group with detectable C-peptide hints towards a positive effect of obtained insulin secretion on the myocardium and aortal endothelium. Further research should investigate the positive effect of obtained C-peptide secretion on the macrovasculature.

5 Bibliography

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019 Nov 1;157:107843.
2. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. N Engl J Med [Internet]. 2017 Apr 13 [cited 2020 Jul 3];376(15):1419–29. Available from: /pmc/articles/PMC5592722/?report=abstract
3. Patterson CC, Harjutsalo V, Rosenbauer J, Neu A, Cinek O, Skrivarhaug T, et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study. Diabetologia [Internet]. 2019 Mar 1 [cited 2020 Jul 3];62(3):408–17. Available from: https://doi.org/10.1007/s00125-018-4763-3
4. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes [Internet]. Vol. 39, Endocrinology and Metabolism Clinics of North America. NIH Public Access; 2010 [cited 2020 Jul 20]. p. 481–97. Available from: /pmc/articles/PMC2925303/?report=abstract
5. Chobot A, Polanska J, Brandt A, Deja G, Glowinska-Olszewska B, Pilecki O, et al. Updated 24-year trend of Type 1 diabetes incidence in children in Poland reveals a sinusoidal pattern and sustained increase. Diabet Med [Internet]. 2017 Sep 1 [cited 2020 Jul 20];34(9):1252–8. Available from: http://doi.wiley.com/10.1111/dme.13345
6. DeFronzo RA, Ferrannini E. Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care [Internet]. 1991 Mar 1 [cited 2020 Jul 23];14(3):173–94. Available from: https://care-1diabetesjournals-1org-10013b5qu4796.han.medunigraz.at/content/14/3/173
7. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes [Internet]. Vol. 391, The Lancet. Lancet Publishing Group; 2018 [cited 2020 Jul 20]. p. 2449–62. Available from: /pmc/articles/PMC6661119/?report=abstract
8. Davis AK, DuBose SN, Haller MJ, Miller KM, DiMeglio LA, Bethin KE, et al. Prevalence of Detectable C-Peptide According to Age at Diagnosis and Duration of Type 1 Diabetes. Diabetes Care [Internet]. 2015 Mar 1 [cited 2021 Jul

20];38(3):476–81. Available from: https://care.diabetesjournals.org/content/38/3/476

9. MC P, GI S. Mechanisms of Insulin Action and Insulin Resistance. Physiol Rev [Internet]. 2018 Oct 1 [cited 2021 Jul 24];98(4):2133–223. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b52801c8.han.medunigraz.at/30067154/
10. Adeva-Andany MM, Martínez-Rodríguez J, González-Lucán M, Fernández-Fernández C, Castro-Quintela E. Insulin resistance is a cardiovascular risk factor in humans. Diabetes Metab Syndr Clin Res Rev. 2019 Mar 1;13(2):1449–55.
11. Snell-Bergeon JK, Hokanson JE, Jensen L, Mackenzie T, Kinney G, Dabelea D, et al. Progression of Coronary Artery Calcification in Type 1 Diabetes The importance of glycemic control. 2003;
12. Barnett R. Type 1 diabetes. Vol. 391, The Lancet. Lancet Publishing Group; 2018. p. 195.
13. Group TDC and CTR. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. N Engl J Med [Internet]. 1993 Sep 30 [cited 2020 Nov 14];329(14):977–86. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM199309303291401
14. Nathan DM. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: Overview. Diabetes Care [Internet]. 2014 Jan [cited 2020 Jul 20];37(1):9–16. Available from: /pmc/articles/PMC3867999/?report=abstract
15. Chiang JL, Maahs DM, Garvey KC, Hood KK, Laffel LM, Weinzimer SA, et al. Type 1 diabetes in children and adolescents: A position statement by the American Diabetes Association [Internet]. Vol. 41, Diabetes Care. American Diabetes Association Inc.; 2018 [cited 2020 Jul 17]. p. 2026–44. Available from: https://doi.org/10.2337/dci18-0023
16. Chiang JL, Kirkman MS, Laffel LMB, Peters AL. Type 1 diabetes through the life span: A position statement of the American Diabetes Association [Internet]. Vol. 37, Diabetes Care. American Diabetes Association Inc.; 2014 [cited 2020 Jul 23]. p. 2034–54. Available from: https://www-1ncbi-1nlm-1nih-1gov-10013b5qu4796.han.medunigraz.at/pmc/articles/PMC5865481/
17. Peters AL, Ahmann AJ, Battelino T, Evert A, Hirsch IB, Murad MH, et al. Diabetes

technology-continuous subcutaneous insulin infusion therapy and continuous glucose monitoring in adults: An endocrine society clinical practice guideline [Internet]. Vol. 101, Journal of Clinical Endocrinology and Metabolism. Endocrine Society; 2016 [cited 2020 Jul 20]. p. 3922–37. Available from: https://academic.oup.com/jcem/article-abstract/101/11/3922/2764917

18. Libby P, Nathan DM, Abraham K, Brunzell JD, Fradkin JE, Haffher SM, et al. Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases Working Group on cardiovascular complications of type 1 diabetes mellitus. In: Circulation [Internet]. Lippincott Williams & Wilkins; 2005 [cited 2020 Jun 18]. p. 3489–93. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.104.529651

19. Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burden AC, Waugh NR, et al. The British Diabetic Association Cohort Study, II: Cause-specific mortality in patients with insulin-treated diabetes mellitus. Diabet Med [Internet]. 1999 Jun 1 [cited 2020 Nov 17];16(6):466–71. Available from: https://onlinelibrary-1wiley-1com-10013b5xf1208.han.medunigraz.at/doi/full/10.1046/j.1464-5491.1999.00076.x

20. Secrest AM, Becker DJ, Kelsey SF, LaPorte RE, Orchard TJ. Cause-specific mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes. Diabetes [Internet]. 2010 Dec 1 [cited 2020 Jul 17];59(12):3216–22. Available from: http://diabetes.diabetesjournals.org

21. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. Diabetologia. 2001;44(2):S14–21.

22. Gregg EW, Garfield S, Cheng YJ, Geiss L, Saydah S, Barker L, et al. Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006: Findings from the National Health Interview Survey. Diabetes Care [Internet]. 2012 Jun [cited 2020 Jul 23];35(6):1252–7. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5qu4796.han.medunigraz.at/22619288/

23. Morgan E, Cardwell CR, Black CJ, Mccance DR, Patterson CC. Excess mortality in Type 1 diabetes diagnosed in childhood and adolescence: a systematic review of population-based cohorts.

24. Livingstone SJ, Levin D, Looker HC, Lindsay RS, Wild SH, Joss N, et al. Estimated life expectancy in a scottish cohort with type 1 diabetes, 2008-2010. JAMA - J Am Med Assoc [Internet]. 2015 Jan 6 [cited 2020 Nov 14];313(1):37–44. Available

from: /pmc/articles/PMC4426486/?report=abstract

25. Huo L, Shaw JE, Wong E, Harding JL, Peeters A, Magliano DJ. Burden of diabetes in Australia: life expectancy and disability-free life expectancy in adults with diabetes. Diabetologia [Internet]. 2016 Jul 1 [cited 2020 Nov 14];59(7):1437–45. Available from: https://link-1springer-1com-10013b5xf07e2.han.medunigraz.at/article/10.1007/s00125-016-3948-x
26. Giannopoulou EZ, Doundoulakis I, Antza C, Christoforidis A, Haidich AB, Kotsis V, et al. Subclinical arterial damage in children and adolescents with type 1 diabetes: A systematic review and meta-analysis [Internet]. Vol. 20, Pediatric Diabetes. Blackwell Publishing Ltd; 2019 [cited 2020 Jul 25]. p. 668–77. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5kj060b.han.medunigraz.at/31173658/
27. Hurks R, Eisinger MJ, Goovaerts I, van Gaal L, Vrints C, Weyler J, et al. Early Endothelial Dysfunction in Young Type 1 Diabetics. Eur J Vasc Endovasc Surg. 2009 May 1;37(5):611–5.
28. Group TDC and CTR. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. N Engl J Med [Internet]. 1993 Sep 30 [cited 2020 Jul 20];329(14):977–86. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM199309303291401
29. Virk SA, Donaghue KC, Cho YH, Benitez-Aguirre P, Hing S, Pryke A, et al. Association Between HbA $_{1c}$ Variability and Risk of Microvascular Complications in Adolescents With Type 1 Diabetes. J Clin Endocrinol Metab [Internet]. 2016 Sep 1 [cited 2020 Nov 14];101(9):3257–63. Available from: https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2015-3604
30. Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? [Internet]. Vol. 20, Indian Journal of Endocrinology and Metabolism. Medknow Publications; 2016 [cited 2020 Dec 17]. p. 546–53. Available from: /pmc/articles/PMC4911847/?report=abstract
31. Groop PH, Thomas MC, Moran JL, Wadèn J, Thorn LM, Mäkinen VP, et al. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. Diabetes [Internet]. 2009 [cited 2020 Nov 14];58(7):1651–8. Available from: /pmc/articles/PMC2699848/?report=abstract
32. Lachin JM, Orchard TJ, Nathan DM. Update on cardiovascular outcomes at 30

years of the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care [Internet]. 2014 Jan [cited 2020 Nov 14];37(1):39–43. Available from: /pmc/articles/PMC3868002/?report=abstract

33. Fullerton B, Jeitler K, Seitz M, Horvath K, Berghold A, Siebenhofer A. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus [Internet]. Vol. 2017, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2014 [cited 2020 Nov 14]. Available from: /pmc/articles/PMC6486147/?report=abstract

34. Lear SA, Hu W, Rangarajan S, Gasevic D, Leong D, Iqbal R, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. Lancet. 2017 Dec 16;390(10113):2643–54.

35. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low Cardiorespiratory Fitness and Physical Inactivity as Predictors of Mortality in Men with Type 2 Diabetes. Ann Intern Med [Internet]. 2000 Apr 18 [cited 2020 Jun 17];132(8):605. Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-132-8-200004180-00002

36. Puciato D, Borysiuk Z, Rozpara M. Quality of life and physical activity in an older working-age population. Clin Interv Aging [Internet]. 2017 Oct 4 [cited 2020 Nov 26];12:1627–34. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5p20045.han.medunigraz.at/29042763/

37. Warburton DER, Nicol CW, Bredin SSD. Health benefits of physical activity: The evidence [Internet]. Vol. 174, CMAJ. CMAJ; 2006 [cited 2020 Jul 18]. p. 801–9. Available from: www.cmaj.ca/cgi/content/full/174/6

38. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, et al. Sedentary Time and Its Association With Risk for Disease Incidence, Mortality, and Hospitalization in Adults. Ann Intern Med [Internet]. 2015 Jan 20 [cited 2020 Nov 19];162(2):123. Available from: http://annals.org/article.aspx?doi=10.7326/M14-1651

39. Wallymahmed ME, Morgan C, Gill G V., MacFarlane IA. Aerobic fitness and hand grip strength in Type 1 diabetes: relationship to glycaemic control and body composition. Diabet Med [Internet]. 2007 Nov 1 [cited 2020 Jul 19];24(11):1296–9. Available from: http://doi.wiley.com/10.1111/j.1464-5491.2007.02257.x

40. Bohn B, Herbst A, Pfeifer M, Krakow D, Zimny S, Kopp F, et al. Impact of physical activity on glycemic control and prevalence of cardiovascular risk factors in adults with type 1 diabetes: A cross-sectional multicenter study of 18,028 patients. Diabetes Care [Internet]. 2015 Aug 1 [cited 2020 Nov 19];38(8):1536–43. Available from: http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-0030/-/DC1.

41. LaPorte RE, Dorman JS, Tajima N, Cruickshanks KJ, Orchard TJ, Cavender DE, et al. Pittsburgh Insulin-Dependent Diabetes Mellitus Morbidity and Mortality Study: Physical Activity and Diabetic Complications. Pediatrics. 1986;78(6).

42. Kriska AM, LaPorte RE, Patrick SL, Kuller LH, Orchard TJ. The association of physical activity and diabetic complications in individuals with insulin-dependent diabetes mellitus: The epidemiology of diabetes complications study-VII. J Clin Epidemiol [Internet]. 1991 [cited 2020 Nov 20];44(11):1207–14. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5xf4084.han.medunigraz.at/1941015/

43. Riddell MC, Perkins BA. Type 1 diabetes and vigorous exercise: Applications of exercise physiology to patient management. Can J Diabetes. 2006 Jan 1;30(1):63–71.

44. Moy CS, Songer TJ, LaPorte RE, Dorman JS, Kriska AM, Orchard TJ, et al. Insulin-dependent Diabetes Mellitus, Physical Activity, and Death. Am J Epidemiol [Internet]. 1993 Jan 1 [cited 2020 Jun 15];137(1):74–81. Available from: https://academic.oup.com/aje/article/303239/Insulin-dependent

45. Imayama I, Plotnikoff RC, Courneya KS, Johnson JA. Determinants of quality of life in adults with type 1 and type 2 diabetes. Health Qual Life Outcomes [Internet]. 2011 Dec 19 [cited 2020 Nov 20];9:115. Available from: /pmc/articles/PMC3258220/?report=abstract

46. Tikkanen-Dolenc H, Wadén J, Forsblom C, Harjutsalo V, Thorn LM, Saraheimo M, et al. Frequent and intensive physical activity reduces risk of cardiovascular events in type 1 diabetes. Diabetologia. 2017 Mar 1;60(3):574–80.

47. Kodama S, Tanaka S, Heianza Y, Fujihara K, Horikawa C, Shimano H, et al. Association between physical activity and risk of all-cause mortality and cardiovascular disease in patients with diabetes: A meta-analysis. Diabetes Care [Internet]. 2013 Feb [cited 2020 Jul 23];36(2):471–9. Available from: /pmc/articles/PMC3554302/?report=abstract

48. Harding JL, Shaw JE, Peeters A, Cartensen B, Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes: Disentangling true associations, detection

bias, and reverse causation. Diabetes Care [Internet]. 2015 Feb 1 [cited 2020 Jul 23];38(2):264–70. Available from: http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-1996/-/DC1.

49. Borghouts LB, Keizer HA. Exercise and insulin sensitivity: A review [Internet]. Vol. 21, International Journal of Sports Medicine. Georg Thieme Verlag Stuttgart ·New York; 2000 [cited 2020 Jul 23]. p. 1–12. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-2000-8847

50. Codella R, Terruzzi I, Luzi L. Why should people with type 1 diabetes exercise regularly? Acta Diabetol [Internet]. 2017 Jul 1 [cited 2020 Nov 21];54(7):615–30. Available from: https://link-1springer-1com-10013b5xf448d.han.medunigraz.at/article/10.1007/s00592-017-0978-x

51. Thorell A, Hirshman MF, Nygren J, Jorfeldt L, Wojtaszewski JFP, Dufresne SD, et al. Exercise and insulin cause GLUT-4 translocation in human skeletal muscle. Am J Physiol - Endocrinol Metab [Internet]. 1999 Oct [cited 2020 Jul 23];277(4 40-4):733–41. Available from: https://journals.physiology.org/doi/abs/10.1152/ajpendo.1999.277.4.E733

52. Perseghin G, Price TB, Petersen KF, Roden M, Cline GW, Gerow K, et al. Increased Glucose Transport–Phosphorylation and Muscle Glycogen Synthesis after Exercise Training in Insulin-Resistant Subjects. N Engl J Med [Internet]. 1996 Oct 31 [cited 2020 Jul 23];335(18):1357–62. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM199610313351804

53. Ding C, Chooi YC, Chan Z, Lo J, Choo J, Ding BTK, et al. Dose-Dependent Effects of Exercise and Diet on Insulin Sensitivity and Secretion. Med Sci Sports Exerc [Internet]. 2019 Oct 1 [cited 2020 Jul 23];51(10):2109–16. Available from: http://journals.lww.com/00005768-201910000-00016

54. Young JC, Enslin J, Kuca B. Exercise intensity and glucose tolerance in trained and nontrained subjects. J Appl Physiol [Internet]. 1989 [cited 2020 Jul 23];67(1):39–43. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5qu48e6.han.medunigraz.at/2668256/

55. Roberto S, Crisafulli A. Consequences of Type 1 and 2 Diabetes Mellitus on the Cardiovascular Regulation During Exercise: A Brief Review. Curr Diabetes Rev [Internet]. 2016 Jun 18 [cited 2020 Jul 19];13(6):560. Available from: /pmc/articles/PMC5684785/?report=abstract

56. Gusso S, Hofman P, Lalande S, Cutfield W, Robinson E, Baldi JC. Impaired stroke

volume and aerobic capacity in female adolescents with type 1 and type 2 diabetes mellitus. Diabetologia [Internet]. 2008 Jul [cited 2020 Nov 20];51(7):1317–20. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5xf4084.han.medunigraz.at/18446317/

57. Niranjan V, McBrayer DG, Ramirez LC, Raskin P, Hsia CCW. Glycemic control and cardiopulmonary function in patients with insulin- dependent diabetes mellitus. Am J Med. 1997 Dec 1;103(6):504–13.

58. Cunningham LN, Labrie C, Soeldner JS, Gleason RE. Resting and exercise hyperemic pulsatile arterial blood flow in insulin-dependent diabetic subjects. Diabetes [Internet]. 1983 [cited 2020 Nov 20];37(7 I):664–9. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5xf4084.han.medunigraz.at/6862111/

59. Villa MP, Montesano M, Barreto M, Pagani J, Stegagno M, Multari G, et al. Diffusing capacity for carbon monoxide in children with type 1 diabetes. Diabetologia [Internet]. 2004 Nov 24 [cited 2020 Dec 14];47(11):1931–5. Available from: https://link-1springer-1com-10013b58i0be9.han.medunigraz.at/article/10.1007/s00125-004-1548-7

60. Bell D, Collier A, Matthews DM, Cooksey EJ, McHardy GJR, Clarke BF. Are reduced lung volumes in IDDM due to defect in connective tissue? Diabetes [Internet]. 1988 Jun 1 [cited 2020 Dec 14];37(6):829–31. Available from: https://diabetes-1diabetesjournals-1org-10013b58i0be9.han.medunigraz.at/content/37/6/829

61. Heyman E, Daussin F, Wieczorek V, Caiazzo R, Matran R, Berthon P, et al. Muscle oxygen supply and use in type 1 diabetes, from ambient air to the mitochondrial respiratory chain: Is there a limiting step? Diabetes Care [Internet]. 2020 Jan 1 [cited 2020 Nov 14];43(1):209–18. Available from: https://care.diabetesjournals.org/content/43/1/209

62. Chimen M, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. Vol. 55, Diabetologia. Springer; 2012. p. 542–51.

63. Codella R, Luzi L, Inverardi L, Ricordi C. The anti-inflammatory effects of exercise in the syndromic thread of diabetes and autoimmunity [Internet]. Vol. 19, European Review for Medical and Pharmacological Sciences. 2015 [cited 2020 Jul 23]. p. 3709–22. Available from: https://www.europeanreview.org/article/9607

64. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al.

Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. Vol. 39, Diabetes Care. American Diabetes Association Inc.; 2016. p. 2065–79.

65. Praet SFE, Van Rooij ESJ, Wijtvliet A, Boonman-De Winter LJM, Enneking T, Kuipers H, et al. Brisk walking compared with an individualised medical fitness programme for patients with type 2 diabetes: A randomised controlled trial. Diabetologia [Internet]. 2008 May [cited 2020 Jul 23];51(5):736–46. Available from: /pmc/articles/PMC2292420/?report=abstract

66. Association AD. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2021. Diabetes Care [Internet]. 2021 Jan 1 [cited 2021 Jul 20];44(Supplement 1):S73–84. Available from: https://care.diabetesjournals.org/content/44/Supplement_1/S73

67. Thabit H, Leelarathna L. Basal insulin delivery reduction for exercise in type 1 diabetes: finding the sweet spot. Diabetologia [Internet]. 2016 Aug 1 [cited 2020 Jul 23];59(8):1628–31. Available from: /pmc/articles/PMC4930462/?report=abstract

68. Frank S, Jbaily A, Hinshaw L, Basu R, Basu A, Szeri AJ. Modeling the acute effects of exercise on insulin kinetics in type 1 diabetes. J Pharmacokinet Pharmacodyn [Internet]. 2018 Dec 1 [cited 2020 Dec 14];45(6):829–45. Available from: https://doi.org/10.1007/s10928-018-9611-z

69. Galassetti P, Riddell MC. Exercise and type 1 diabetes (T1DM). Compr Physiol [Internet]. 2013 [cited 2020 Nov 24];3(3):1309–36. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5xf4ff4.han.medunigraz.at/23897688/

70. Riddell MC, Zaharieva DP, Tansey M, Tsalikian E, Admon G, Li Z, et al. Individual glucose responses to prolonged moderate intensity aerobic exercise in adolescents with type 1 diabetes: The higher they start, the harder they fall. Pediatr Diabetes [Internet]. 2018 Dec 13 [cited 2020 Nov 24];20(1):pedi.12799. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/pedi.12799

71. Gawrecki A, Zozulinska-Ziolkiewicz D, Matejko B, Hohendorff J, Malecki MT, Klupa T. Safe Completion of a Trail Running Ultramarathon by Four Men with Type 1 Diabetes. Diabetes Technol Ther [Internet]. 2018 Feb 1 [cited 2020 Nov 24];20(2):147–52. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5xf4ff4.han.medunigraz.at/29293025/

72. Matejko B, Benbenek-Klupa T, Malecki MT, Klupa T. Type 1 Diabetes and Combat Sports: Improvement in Glycemic Control With Gained Experience [Internet]. Vol.

12, Journal of Diabetes Science and Technology. SAGE Publications Inc.; 2018 [cited 2020 Nov 24]. p. 1088–9. Available from: https://www-1ncbi-1nlm-1nih-1gov-10013b5xf4ff4.han.medunigraz.at/pmc/articles/PMC6134605/

73. Klupa T, Hohendorff J, Benbenek-Klupa T, Matejko B, Malecki MT. Insulin pump settings and glucose patterns during a 1008-km non-stop bicycle race in a patient with type 1 diabetes mellitus. Acta Diabetol [Internet]. 2019 May 9 [cited 2020 Nov 24];56(5):593–5. Available from: https://www-1ncbi-1nlm-1nih-1gov-10013b5xf4ff4.han.medunigraz.at/pmc/articles/PMC6451704/

74. Moser O, Riddell MC, Eckstein ML, Adolfsson P, Rabasa-Lhoret R, van den Boom L, et al. Glucose management for exercise using continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) systems in type 1 diabetes: position statement of the European Association for the Study of Diabetes (EASD) and of the International Society for Pediatric and Adolescent Diabetes (ISPAD) endorsed by JDRF and supported by the American Diabetes Association (ADA). Diabetologia [Internet]. 2020 Dec 1 [cited 2020 Nov 26];63(12):2501–20. Available from: https://link.springer.com/article/10.1007/s00125-020-05263-9

75. Plotnikoff RC, Taylor LM, Wilson PM, Courneya KS, Sigal RJ, Birkett N, et al. Factors associated with physical activity in Canadian adults with diabetes. Med Sci Sports Exerc [Internet]. 2006 Aug 1 [cited 2020 Jul 23];38(8):1526–34. Available from: https://europepmc.org/article/med/16888470

76. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care [Internet]. 2008 Nov [cited 2020 Jul 23];31(11):2108–9. Available from: /pmc/articles/PMC2571055/?report=abstract

77. MacDonald MJ. Postexercise late-onset hypoglycemia in insulin-dependent diabetic patients. Diabetes Care [Internet]. 1987 Sep 1 [cited 2020 Jul 19];10(5):584–8. Available from: https://care-1diabetesjournals-1org-10013b5qu36bf.han.medunigraz.at/content/10/5/584

78. Cryer PE. Mechanisms of Hypoglycemia-Associated Autonomic Failure in Diabetes. N Engl J Med [Internet]. 2013 Jul 25 [cited 2020 Nov 23];369(4):362–72. Available from: https://www-1nejm-1org-10013b5xf49b1.han.medunigraz.at/doi/10.1056/NEJMra1215228

79. Dagogo-Jack SE, Craft S, Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent

hypoglycemia. J Clin Invest. 1993 Mar 1;91(3):819–28.

80. Cryer PE. Hypoglycemia in type 1 diabetes mellitus [Internet]. Vol. 39, Endocrinology and Metabolism Clinics of North America. Endocrinol Metab Clin North Am; 2010 [cited 2020 Nov 23]. p. 641–54. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5xf49b1.han.medunigraz.at/20723825/
81. Cryer PE. The barrier of hypoglycemia in diabetes [Internet]. Vol. 57, Diabetes. American Diabetes Association; 2008 [cited 2020 Nov 23]. p. 3169–76. Available from: https://www-1ncbi-1nlm-1nih-1gov-10013b5xf4a81.han.medunigraz.at/pmc/articles/PMC2584119/
82. DUBÉ M-C, WEISNAGEL SJ, PRUD'HOMME D, LAVOIE C. Exercise and Newer Insulins: How Much Glucose Supplement to Avoid Hypoglycemia? Med Sci Sport Exerc [Internet]. 2005 Aug [cited 2020 Nov 21];37(8):1276–82. Available from: http://journals.lww.com/00005768-200508000-00004
83. Zaharieva DP, Riddell MC. Prevention of exercise-associated dysglycemia: A case study-based approach. Diabetes Spectr [Internet]. 2015 Feb 1 [cited 2020 Jul 23];28(1):55–62. Available from: https://spectrum.diabetesjournals.org/content/28/1/55
84. Rabasa-Lhoret R, Bourque J, Ducros F, Chiasson JL. Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal-bolus insulin regimen (ultralente-lispro). Diabetes Care [Internet]. 2001 Apr 1 [cited 2020 Nov 21];24(4):625–30. Available from: https://care.diabetesjournals.org/content/24/4/625
85. Yardley JE, Iscoe KE, Sigal RJ, Kenny GP, Perkins BA, Riddell MC. Insulin Pump Therapy is associated with Less Post-Exercise Hyperglycemia than multiple daily injections: An observational study of physically active type 1 diabetes patients. Diabetes Technol Ther [Internet]. 2013 Jan 1 [cited 2020 Nov 21];15(1):84–8. Available from: https://www-1liebertpub-1com-10013b5xf4412.han.medunigraz.at/doi/abs/10.1089/dia.2012.0168
86. Lumb AN, Gallen IW. Diabetes management for intense exercise. Curr Opin Endocrinol Diabetes Obes [Internet]. 2009 Apr [cited 2020 Jul 19];16(2):150–5. Available from: http://journals.lww.com/01266029-200904000-00010
87. Turner D, Gray BJ, Luzio S, Dunseath G, Bain SC, Hanley S, et al. Similar magnitude of post-exercise hyperglycemia despite manipulating resistance exercise intensity in type 1 diabetes individuals. Scand J Med Sci Sports [Internet]. 2016 Apr

1 [cited 2020 Dec 18];26(4):404–12. Available from: http://doi.wiley.com/10.1111/sms.12472

88. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's guide to cardiopulmonary exercise testing in adults: A scientific statement from the American heart association [Internet]. Vol. 122, Circulation. Lippincott Williams & Wilkins; 2010 [cited 2020 Jul 23]. p. 191–225. Available from: https://www.ahajournals.org/doi/10.1161/CIR.0b013e3181e52e69

89. Ross R, Blair SN, Arena R, Church TS, Després JP, Franklin BA, et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement from the American Heart Association. Circulation [Internet]. 2016 Dec 13 [cited 2020 Dec 18];134(24):e653–99. Available from: http://ahajournals.org

90. Regensteiner JG. Type 2 Diabetes Mellitus and Cardiovascular Exercise Performance. Vol. 5, Reviews in Endocrine & Metabolic Disorders. Kluwer Academic Publishers; 2004.

91. Imboden MT, Harber MP, Whaley MH, Finch WH, Bishop DL, Kaminsky LA. Cardiorespiratory Fitness and Mortality in Healthy Men and Women. J Am Coll Cardiol. 2018 Nov 6;72(19):2283–92.

92. Mezzani A. Cardiopulmonary exercise testing: Basics of methodology and measurements. In: Annals of the American Thoracic Society [Internet]. American Thoracic Society; 2017 [cited 2020 Jul 18]. p. S3–11. Available from: http://www.atsjournals.org/doi/10.1513/AnnalsATS.201612-997FR

93. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens [Internet]. 2012 Mar [cited 2020 Jul 25];30(3):445–8. Available from: http://journals.lww.com/00004872-201203000-00001

94. Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O'Rourke MF. Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. Circulation [Internet]. 1983 Jul [cited 2020 Jul 28];68(1):50–8. Available from: https://www.ahajournals.org/doi/10.1161/01.CIR.68.1.50

95. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications on behalf of the European Network for Non-invasive Investigation of

Large Arteries. 2006 [cited 2020 Jul 25]; Available from: https://academic.oup.com/eurheartj/article-abstract/27/21/2588/2887386

96. Cecelja M, Chowienczyk P. Role of arterial stiffness in cardiovascular disease. JRSM Cardiovasc Dis [Internet]. 2012 Jul 1 [cited 2020 Nov 24];1(4):1–10. Available from: http://journals.sagepub.com/doi/10.1258/cvd.2012.012016

97. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness. A Systematic Review and Meta-Analysis. J Am Coll Cardiol [Internet]. 2010 Mar 30 [cited 2020 Jul 28];55(13):1318–27. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5kj0e6e.han.medunigraz.at/20338492/

98. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, et al. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA - J Am Med Assoc [Internet]. 2012 Aug 29 [cited 2020 Aug 20];308(9):875–81. Available from: /pmc/articles/PMC3594687/?report=abstract

99. Najjar SS, Scuteri A, Shetty V, Wright JG, Muller DC, Fleg JL, et al. Pulse Wave Velocity Is an Independent Predictor of the Longitudinal Increase in Systolic Blood Pressure and of Incident Hypertension in the Baltimore Longitudinal Study of Aging. J Am Coll Cardiol [Internet]. 2008 Apr 8 [cited 2020 Aug 20];51(14):1377–83. Available from: /pmc/articles/PMC2771854/?report=abstract

100. Mattace-Raso FUS, Van Der Cammen TJM, Hofman A, Van Popele NM, Bos ML, Schalekamp MADH, et al. Arterial stiffness and risk of coronary heart disease and stroke: The Rotterdam Study. Circulation [Internet]. 2006 Feb 7 [cited 2020 Aug 20];113(5):657–63. Available from: http://www.circulationaha.org

101. Sun Z. Aging, arterial stiffness, and hypertension. Hypertension [Internet]. 2015 Feb 21 [cited 2020 Jul 28];65(2):252–6. Available from: https://www-1ncbi-1nlm-1nih-1gov-10013b5kj0e6e.han.medunigraz.at/pmc/articles/PMC4288978/

102. Wang P, Xu YY, Lv TT, Guan SY, Li XM, Li XP, et al. Subclinical Atherosclerosis in Patients With Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis [Internet]. Vol. 70, Angiology. SAGE Publications Inc.; 2019 [cited 2020 Nov 18]. p. 141–59. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5xf1a6d.han.medunigraz.at/30009613/

103. Bjornstad P, Pyle L, Nguyen N, Snell-Bergeon JK, Bishop FK, Wadwa RP, et al. Achieving International Society for Pediatric and Adolescent Diabetes and American Diabetes Association clinical guidelines offers cardiorenal protection for

youth with type 1 diabetes. Pediatr Diabetes [Internet]. 2015 Feb 1 [cited 2020 Jul 25];16(1):22–30. Available from: /pmc/articles/PMC5426809/?report=abstract

104. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. Circulation [Internet]. 2000 Sep 12 [cited 2021 Jan 28];102(11):1270–5. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b58m033c.han.medunigraz.at/10982542/

105. Perissiou M, Bailey TG, Windsor M, Nam MCY, Greaves K, Leicht AS, et al. Effects of exercise intensity and cardiorespiratory fitness on the acute response of arterial stiffness to exercise in older adults. Eur J Appl Physiol [Internet]. 2018 Aug 1 [cited 2020 Nov 24];118(8):1673–88. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5xf513b.han.medunigraz.at/29850932/

106. Tordi N, Mourot L, Colin E, Regnard J. Intermittent versus constant aerobic exercise: Effects on arterial stiffness. Eur J Appl Physiol [Internet]. 2010 Mar 19 [cited 2020 Nov 25];108(4):801–9. Available from: https://link-1springer-1com-10013b5xf52a3.han.medunigraz.at/article/10.1007/s00421-009-1285-1

107. Hanssen H, Nussbaumer M, Moor C, Cordes M, Schindler C, Schmidt-Trucksäss A. Acute effects of interval versus continuous endurance training on pulse wave reflection in healthy young men. Atherosclerosis. 2015 Feb 1;238(2):399–406.

108. Gkaliagkousi E, Gavriilaki E, Nikolaidou B, Triantafyllou G, Douma S. Exercise-Induced Pulse Wave Velocity Changes in Untreated Patients With Essential Hypertension: The Effect of an Angiotensin Receptor Antagonist. J Clin Hypertens. 2014;16(7):482–7.

109. Shim CY, Yang W-I, Park S, Kang M-K, Ko Y-G, Choi D, et al. Overweight and Its Association With Aortic Pressure Wave Reflection After Exercise. Am J Hypertens [Internet]. 2011 Oct 1 [cited 2020 Nov 25];24(10):1136–42. Available from: https://academic.oup.com/ajh/article-lookup/doi/10.1038/ajh.2011.121

110. Schultz MG, La Gerche A, Sharman JE. Blood Pressure Response to Exercise and Cardiovascular Disease [Internet]. Vol. 19, Current Hypertension Reports. Current Medicine Group LLC 1; 2017 [cited 2020 Nov 25]. p. 1–7. Available from: https://link-1springer-1com-10013b5xf533e.han.medunigraz.at/article/10.1007/s11906-017-0787-1

111. Wong TY, Klein R, Richey Sharrett A, Couper DJ, Klein BEK, Liao DP, et al. Cerebral white matter lesions, retinopathy, and incident clinical stroke. J Am Med Assoc [Internet]. 2002 Jul 3 [cited 2020 Aug 23];288(1):67–74. Available from:

www.jama.com

112. Seidelmann SB, Claggett B, Bravo PE, Gupta A, Farhad H, Klein BE, et al. Retinal Vessel Calibers in Predicting Long-Term Cardiovascular Outcomes: The Atherosclerosis Risk in Communities Study. Circulation [Internet]. 2016 Nov 1 [cited 2021 Jun 10];134(18):1328–38. Available from: http://ahajournals.org

113. Ikram MK, De Jong FJ, Bos MJ, Vingerling JR, Hofman A, Koudstaal PJ, et al. Retinal vessel diameters and risk of stroke: The Rotterdam Study. Neurology [Internet]. 2006 May 9 [cited 2020 Aug 23];66(9):1339–43. Available from: https://n-1neurology-1org-10013b5hq0a5b.han.medunigraz.at/content/66/9/1339

114. Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Tielsch JM, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women: The Atherosclerosis Risk in Communities Study. J Am Med Assoc [Internet]. 2002 Mar 6 [cited 2021 Jun 10];287(9):1153–9. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5dz02d8.han.medunigraz.at/11879113/

115. Wang JJ, Liew G, Klein R, Rochtchina E, Knudtson MD, Klein BEK, et al. Retinal vessel diameter and cardiovascular mortality: Pooled data analysis from two older populations. Eur Heart J [Internet]. 2007 Aug [cited 2021 Jun 10];28(16):1984–92. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5dz02d8.han.medunigraz.at/17626032/

116. Klein R, Klein BEK, Moss SE, Wong TY, Hubbard L, Cruickshanks KJ, et al. Retinal Vascular Abnormalities in Persons with Type 1 Diabetes: The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVIII. Ophthalmology. 2003;110(11):2118–25.

117. Grauslund J, Hodgson L, Kawasaki R, Green A, Sjølie AK, Wong TY. Retinal vessel calibre and micro- and macrovascular complications in type 1 diabetes. Diabetologia [Internet]. 2009 Oct 18 [cited 2021 Jun 11];52(10):2213–7. Available from: https://link-1springer-1com-10013b5dz04b5.han.medunigraz.at/article/10.1007/s00125-009-1459-8

118. Ogagarue ER, Lutsey PL, Klein R, Klein BE, Folsom AR. Association of ideal cardiovascular health metrics and retinal microvascular findings: the Atherosclerosis Risk in Communities Study. J Am Heart Assoc [Internet]. 2013 [cited 2020 Aug 23];2(6). Available from: /pmc/articles/PMC3886782/?report=abstract

119. Hanssen H, Nickel T, Drexel V, Hertel G, Emslander I, Sisic Z, et al. Exercise-induced alterations of retinal vessel diameters and cardiovascular risk reduction in

obesity. Atherosclerosis. 2011 Jun 1;216(2):433–9.

120. Streese L, Guerini C, Bühlmayer L, Lona G, Hauser C, Bade S, et al. Physical activity and exercise improve retinal microvascular health as a biomarker of cardiovascular risk: A systematic review. Vol. 315, Atherosclerosis. Elsevier Ireland Ltd; 2020. p. 33–42.

121. Keel S, Itsiopoulos C, Koklanis K, Vukicevic M, Cameron F, Brazionis L. Physical activity, sedentary behaviors, and retinal vascular caliber in children and adolescents with type 1 diabetes. Asia-Pacific J Ophthalmol [Internet]. 2016 [cited 2021 Jun 11];5(3):180–4. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5dz04b5.han.medunigraz.at/27003733/

122. Louwies T, Int Panis L, Alders T, Bonné K, Goswami N, Nawrot TS, et al. Microvascular reactivity in rehabilitating cardiac patients based on measurements of retinal blood vessel diameters. Microvasc Res. 2019 Jul 1;124:25–9.

123. Wolf A, Zalpour C, Theilmeier G, Wang BY, Ma A, Anderson B, et al. Dietary L-arginine supplementation normalizes platelet aggregation in hypercholesterolemic humans. J Am Coll Cardiol [Internet]. 1997 Mar 1 [cited 2020 Aug 16];29(3):479–85. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5kj3c20.han.medunigraz.at/9060881/

124. Kubes P, Suzuki M, Granger DN. Nitric oxide: An endogenous modulator of leukocyte adhesion. Proc Natl Acad Sci U S A [Internet]. 1991 Jun 1 [cited 2020 Aug 16];88(11):4651–5. Available from: /pmc/articles/PMC51723/?report=abstract

125. Böger RH, Bode-Böger SM, Kienke S, Stan AC, Nafe R, Frölich JC. Dietary L-arginine decreases myointimal cell proliferation and vascular monocyte accumulation in cholesterol-fed rabbits. Atherosclerosis. 1998 Jan 1;136(1):67–77.

126. Hogg N, Kalyanaraman B, Joseph J, Struck A, Parthasarathy S. Inhibition of low-density lipoprotein oxidation by nitric oxide Potential role in atherogenesis. FEBS Lett [Internet]. 1993 Nov 15 [cited 2020 Aug 16];334(2):170–4. Available from: http://doi.wiley.com/10.1016/0014-5793%2893%2981706-6

127. Epstein FH, Moncada S, Higgs A. The L-Arginine-Nitric Oxide Pathway. N Engl J Med [Internet]. 1993 Dec 30 [cited 2020 Aug 16];329(27):2002–12. Available from: http://www.nejm.org/doi/abs/10.1056/NEJM199312303292706

128. Abhary S, Kasmeridis N, Burdon KP, Kuot A, Whiting MJ, Wai PY, et al. Diabetic retinopathy is associated with elevated serum asymmetric and symmetric dimethylarginines. Diabetes Care [Internet]. 2009 Nov [cited 2020 Aug

20];32(11):2084–6. Available from: /pmc/articles/PMC2768206/?report=abstract

129. Hanai K, Babazono T, Nyumura I, Toya K, Tanaka N, Tanaka M, et al. Asymmetric dimethylarginine is closely associated with the development and progression of nephropathy in patients with type 2 diabetes. Nephrol Dial Transplant [Internet]. 2009 Jun 1 [cited 2020 Aug 20];24(6):1884–8. Available from: https://academic.oup.com/ndt/article/24/6/1884/1840274

130. Stojanovic I, Djordjevic G, Pavlovic R, Djordjevic V, Pavlovic D, Cvetkovic T, et al. The importance of L-arginine metabolism modulation in diabetic patients with distal symmetric polyneuropathy. 2012 [cited 2020 Aug 20]; Available from: http://dx.doi.org/10.1016/j.jns.2012.09.026

131. Sena CM, Pereira AM, Seiça R. Endothelial dysfunction-A major mediator of diabetic vascular disease. 2013 [cited 2020 Aug 20]; Available from: http://dx.doi.org/10.1016/j.bbadis.2013.08.006

132. Janes F, Cifù A, Pessa ME, Domenis R, Gigli GL, Sanvilli N, et al. ADMA as a possible marker of endothelial damage. A study in young asymptomatic patients with cerebral small vessel disease. Sci Rep [Internet]. 2019 Dec 1 [cited 2020 Aug 16];9(1). Available from: /pmc/articles/PMC6775279/?report=abstract

133. Liu J, Li C, Chen W, He K, Ma H, Ma B, et al. Relationship between serum asymmetric dimethylarginine level and microvascular complications in diabetes mellitus: A meta-analysis. Biomed Res Int [Internet]. 2019 [cited 2020 Aug 20];2019. Available from: /pmc/articles/PMC6413490/?report=abstract

134. Willeit P, Freitag DF, Laukkanen JA, Chowdhury S, Gobin R, Mayr M, et al. Asymmetric dimethylarginine and cardiovascular risk: Systematic review and meta-analysis of 22 prospective studies. J Am Heart Assoc [Internet]. 2015 [cited 2020 Aug 16];4(6). Available from: /pmc/articles/PMC4599532/?report=abstract

135. Sibal L, C Agarwal S, D Home P, H Boger R. The Role of Asymmetric Dimethylarginine (ADMA) in Endothelial Dysfunction and Cardiovascular Disease. Curr Cardiol Rev [Internet]. 2010 Apr 22 [cited 2020 Aug 16];6(2):82–90. Available from: /pmc/articles/PMC2892080/?report=abstract

136. Gać P. Cite as the Creative Commons Attribution 3.0 Unported (CC BY 3.0) Address for correspondence Funding sources. Adv Clin Exp Med [Internet]. 2020 [cited 2020 Aug 16];29(1):63–70. Available from: https://creativecommons.org/licenses/by/3.0/

137. Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. Pro- and anti-

inflammatory cytokine balance in strenuous exercise in humans. J Physiol [Internet]. 1999 Feb 15 [cited 2020 Nov 27];515(1):287–91. Available from: /pmc/articles/PMC2269132/?report=abstract

138. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: Regulation, integration, and adaptation [Internet]. Vol. 80, Physiological Reviews. American Physiological Society; 2000 [cited 2020 Nov 27]. p. 1055–81. Available from: https://journals-1physiology-1org-10013b5p2019d.han.medunigraz.at/doi/abs/10.1152/physrev.2000.80.3.1055

139. Hiscock N, Chan MHS, Bisucci T, Darby IA, Febbraio MA. Skeletal myocytes are a source of interleukin-6 mRNA expression and protein release during contraction: evidence of fiber type specificity. FASEB J [Internet]. 2004 Jun [cited 2020 Nov 27];18(9):992–4. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5p20335.han.medunigraz.at/15059966/

140. Fischer CP. Interleukin-6 in acute exercise and training: what is the biological relevance? Vol. 12, Exerc. Immunol. Rev. 2006.

141. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: Focus on muscle-derived interleukin-6 [Internet]. Vol. 88, Physiological Reviews. American Physiological Society; 2008 [cited 2020 Nov 28]. p. 1379–406. Available from: www.prv.org

142. Ridker PM, Hennekens C, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in diabetes. Vol. 8, The New England Journal of Medicine. 2000.

143. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma Concentration of Interleukin-6 and the Risk of Future Myocardial Infarction Among Apparently Healthy Men. Circulation [Internet]. 2000 Apr 18 [cited 2020 Nov 27];101(15):1767–72. Available from: https://www.ahajournals.org/doi/10.1161/01.CIR.101.15.1767

144. Volpato S, Guralnik JM, Ferrucci L, Balfour J, Chaves P, Fried LP, et al. Cardiovascular Disease, Interleukin-6, and Risk of Mortality in Older Women. Circulation [Internet]. 2001 Feb 20 [cited 2020 Nov 27];103(7):947–53. Available from: https://www.ahajournals.org/doi/10.1161/01.CIR.103.7.947

145. Huh JY. The role of exercise-induced myokines in regulating metabolism [Internet]. Vol. 41, Archives of Pharmacal Research. Pharmaceutical Society of Korea; 2018 [cited 2020 Nov 28]. p. 14–29. Available from: https://link-1springer-1com-

10013b5p20513.han.medunigraz.at/article/10.1007/s12272-017-0994-y

146. Steensberg A, Fischer CP, Keller C, Møller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. Am J Physiol - Endocrinol Metab [Internet]. 2003 Aug 1 [cited 2020 Dec 19];285(2 48-2):433–7. Available from: http://www.ajpendo.orge433

147. Steinbacher P, Eckl P. Impact of oxidative stress on exercising skeletal muscle [Internet]. Vol. 5, Biomolecules. MDPI AG; 2015 [cited 2020 Nov 28]. p. 356–77. Available from: /pmc/articles/PMC4496677/?report=abstract

148. Ellingsgaard H, Hauselmann I, Schuler B, Habib AM, Baggio LL, Meier DT, et al. Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. Nat Med [Internet]. 2011 Nov [cited 2020 Nov 27];17(11):1481–9. Available from: /pmc/articles/PMC4286294/?report=abstract

149. Ellingsgaard H, Ehses JA, Hammar EB, Van Lommel L, Quintens R, Martens G, et al. Interleukin-6 regulates pancreatic α-cell mass expansion. Proc Natl Acad Sci U S A [Internet]. 2008 Sep 2 [cited 2020 Nov 27];105(35):13163–8. Available from: /pmc/articles/PMC2529061/?report=abstract

150. Krause M da S, Bittencourt A, de Bittencourt PIH, McClenaghan NH, Flatt PR, Murphy C, et al. Physiological concentrations of interleukin-6 directly promote insulin secretion, signal transduction, nitric oxide release, and redox status in a clonal pancreatic β-cell line and mouse islets. J Endocrinol [Internet]. 2012 Sep 1 [cited 2020 Nov 28];214(3):301–11. Available from: www.endocrinology-journals.org

151. Suzuki T, Imai J, Yamada T, Ishigaki Y, Kaneko K, Uno K, et al. Interleukin-6 enhances glucose-stimulated insulin secretion from pancreatic β-cells: Potential involvement of the PLC-IP3-dependent pathway. Diabetes [Internet]. 2011 Feb [cited 2020 Nov 28];60(2):537–47. Available from: /pmc/articles/PMC3028353/?report=abstract

152. van Hall G, Steensberg A, Sacchetti M, Fischer C, Keller C, Schjerling P, et al. Interleukin-6 Stimulates Lipolysis and Fat Oxidation in Humans. J Clin Endocrinol Metab [Internet]. 2003 Jul 1 [cited 2020 Nov 28];88(7):3005–10. Available from: https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2002-021687

153. Knudsen JG, Murholm M, Carey AL, Biensø RS, Basse AL, Allen TL, et al. Role of IL-6 in exercise training- and cold-induced UCP1 expression in subcutaneous white

adipose tissue. PLoS One [Internet]. 2014 Jan 8 [cited 2020 Nov 29];9(1). Available from: /pmc/articles/PMC3885654/?report=abstract

154. Fischer CP, Hiscock NJ, Penkowa M, Basu S, Vessby B, Kallner A, et al. Supplementation with vitamins C and E inhibits the release of interleukin-6 from contracting human skeletal muscle. J Physiol [Internet]. 2004 Jul 15 [cited 2020 Nov 27];558(2):633–45. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5p20310.han.medunigraz.at/15169848/

155. Devaraj S, Glaser N, Griffen S, Wang-Polagruto J, Miguelino E, Jialal I. Increased monocytic activity and biomarkers of inflammation in patients with type 1 diabetes. Diabetes [Internet]. 2006 Mar 1 [cited 2020 Nov 27];55(3):774–9. Available from: https://diabetes.diabetesjournals.org/content/55/3/774

156. Yao Y, Li R, Du J, Long L, Li X, Luo N. Interleukin-6 and Diabetic Retinopathy: A Systematic Review and Meta-Analysis. Curr Eye Res [Internet]. 2019 May 4 [cited 2020 Nov 29];44(5):564–74. Available from: https://www-1tandfonline-1com-10013b5p20944.han.medunigraz.at/doi/abs/10.1080/02713683.2019.1570274

157. De Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Vol. 362, Lancet. Elsevier Limited; 2003. p. 316–22.

158. Federico C. Natriuretic Peptide system and cardiovascular disease. Heart Views [Internet]. 2010 Mar [cited 2020 Dec 22];11(1):10–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21042458

159. Maisel A. The coming of age of natriuretic peptides: The emperor does have clothes! Vol. 47, Journal of the American College of Cardiology. Elsevier USA; 2006. p. 61–4.

160. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America [Internet]. Vol. 136, Circulation. Lippincott Williams and Wilkins; 2017 [cited 2020 Dec 7]. p. e137–61. Available from: http://ahajournals.org

161. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [Internet]. Vol. 37, European Heart Journal. Oxford University Press; 2016 [cited 2020 Dec 7]. p. 2129-2200m. Available from:

https://academic.oup.com/eurheartj/article/37/27/2129/1748921

162. Maries L, Manitiu I. Diagnostic and prognostic values of B-type natriuretic peptides (BNP) and N-terminal fragment brain natriuretic peptides (NT-pro-BNP) [Internet]. Vol. 24, Cardiovascular Journal of Africa. Clinics Cardive Publishing (Pty) Ltd.; 2013 [cited 2020 Dec 22]. p. 286–9. Available from: /pmc/articles/PMC3807675/?report=abstract

163. McKenna K, Smith D, Sherlock M, Moore K, O'Brien E, Tormey W, et al. Elevated plasma concentrations of atrial and brain natriuretic peptide in type 1 diabetic subjects. Ir J Med Sci [Internet]. 2005 [cited 2020 Dec 7];174(3):53–7. Available from: https://link-1springer-1com-10013b56w12e3.han.medunigraz.at/article/10.1007/BF03169149

164. Salem M, El Behery S, Adly A, Khalil D, El Hadidi E. Early predictors of myocardial disease in children and adolescents with type 1 diabetes mellitus. Pediatr Diabetes [Internet]. 2009 Dec 1 [cited 2020 Dec 7];10(8):513–21. Available from: http://doi.wiley.com/10.1111/j.1399-5448.2009.00517.x

165. Kır M, Cetin B, Demir K, Yılmaz N, Kızılca O, Demircan T, et al. Can ambulatory blood pressure monitoring detect early diastolic dysfunction in children with type 1 diabetes mellitus: correlations with B-type natriuretic peptide and tissue Doppler findings. Pediatr Diabetes [Internet]. 2016 Feb 1 [cited 2020 Dec 7];17(1):21–7. Available from: http://doi.wiley.com/10.1111/pedi.12234

166. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, et al. Utility of B-Natriuretic Peptide in Detecting Diastolic Dysfunction. Circulation [Internet]. 2002 Feb 5 [cited 2020 Dec 7];105(5):595–601. Available from: https://www.ahajournals.org/doi/10.1161/hc0502.103010

167. Yazici M, Ozdemir K, Gonen MS, Kayrak M, Ulgen MS, Duzenli MA, et al. Is There Any Relationship between Metabolic Parameters and Left Ventricular Functions in Type 2 Diabetic Patients without Evident Heart Disease? Echocardiography [Internet]. 2008 Aug 1 [cited 2020 Dec 7];25(7):675–82. Available from: http://doi.wiley.com/10.1111/j.1540-8175.2008.00690.x

168. Maeder MT, Thompson BR, Kaye DM. Inverse Association Between Myocardial B-Type Natriuretic Peptide Release and Functional Capacity in Healthy Humans. Hear Lung Circ. 2018 Aug 1;27(8):995–1003.

169. Maeder M, Wolber T, Rickli H, Myers J, Hack D, Riesen W, et al. B-type natriuretic peptide kinetics and cardiopulmonary exercise testing in heart failure. Int J Cardiol

[Internet]. 2007 Sep 3 [cited 2021 Jan 15];120(3):391–8. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5r7051c.han.medunigraz.at/17182129/

170. Donnellan E, Phelan D. Biomarkers of Cardiac Stress and Injury in Athletes: What Do They Mean? [Internet]. Vol. 15, Current Heart Failure Reports. Current Science Inc.; 2018 [cited 2021 Jan 23]. p. 116–22. Available from: https://doi.org/10.1007/s11897-018-0385-9

171. Krupička J, Janota T, Kasalová Z, Hradec J. Effect of Short-Term Maximal Exercise on BNP Plasma Levels in Healthy Individuals. 2010 [cited 2021 Jun 20]; Available from: www.biomed.cas.cz/physiolresPhysiol.Res.59:625-628,2010

172. Fudim M, Kelly JP, Jones AD, AbouEzzeddine OF, Ambrosy AP, Greene SJ, et al. Are existing and emerging biomarkers associated with cardiorespiratory fitness in patients with chronic heart failure? Am Heart J. 2020 Feb 1;220:97–107.

173. Smart NA, Steele M. Systematic review of the effect of aerobic and resistance exercise training on systemic brain natriuretic peptide (BNP) and N-terminal BNP expression in heart failure patients [Internet]. Vol. 140, International Journal of Cardiology. Elsevier Ireland Ltd; 2010 [cited 2021 Jan 14]. p. 260–5. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5r7037b.han.medunigraz.at/19664831/

174. Komatsu WR, Neto TLB, Chacra AR, Dib SA. Aerobic exercise capacity and pulmonary function in athletes with and without type 1 diabetes. Diabetes Care [Internet]. 2010 Dec [cited 2021 Jan 12];33(12):2555–7. Available from: /pmc/articles/PMC2992189/?report=abstract

175. Deftereos S, Bouras G, Tsounis D, Papadimitriou C, Hatzis G, Raisakis K, et al. Association of asymmetric dimethylarginine levels with treadmill-stress-test-derived prognosticators. Clin Biochem. 2014 May 1;47(7–8):593–8.

176. Seljeflot I, Nilsson BB, Westheim AS, Bratseth V, Arnesen H. The L-arginine-asymmetric dimethylarginine ratio is strongly related to the severity of chronic heart failure. No effects of exercise training. J Card Fail. 2011 Feb 1;17(2):135–42.

177. Tanahashi K, Akazawa N, Miyaki A, Choi Y, Ra SG, Matsubara T, et al. Plasma ADMA concentrations associate with aerobic fitness in postmenopausal women. In: Life Sciences. Elsevier Inc.; 2014. p. 30–3.

178. Pawlak-Chaouch M, Boissière J, Munyaneza D, Tagougui S, Gamelin FX, Cuvelier G, et al. Plasma asymmetric dimethylarginine concentrations are not related to

differences in maximal oxygen uptake in endurance trained and untrained men. Exp Physiol [Internet]. 2019 Feb 1 [cited 2021 Jan 5];104(2):254–63. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5on0c4a.han.medunigraz.at/30561141/

179. Chapman BP, Khan A, Harper M, Stockman D, Fiscella K, Walton J, et al. Gender, Race/Ethnicity, Personality, and Interleukin-6 in Urban Primary Care Patients. Brain Behav Immun [Internet]. 2009 Jul [cited 2021 Jul 30];23(5):636. Available from: /pmc/articles/PMC2694851/

180. Haapala EA, Lee E, Laukkanen JA. Associations of cardiorespiratory fitness, physical activity, and BMI with arterial health in middle-aged men and women. Physiol Rep [Internet]. 2020 May 1 [cited 2021 Jun 13];8(10). Available from: /pmc/articles/PMC7243195/