Aus der Abteilung für Kinderkardiologie und Pädiatrische Intensivmedizin

der Ludwig-Maximilians-Universität München

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Bedeutung von arteriellen Gefäßeigenschaften bei Patienten mit angeborenen Herzerkrankungen oder mit während der Kindheit erworbenen kardiovaskulären Risikofaktoren

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Relevance of arterial characteristics in patients with congenital heart disease or risk factors acquired during childhood

Kumulative Habilitationsschrift zur Erlangung der Venia Legendi im Fach Pädiatrie

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τὸ εὔδαιμον τὸ ἐλεύθερον, τὸ δ' ἐλεύθερον τὸ εὔψυχον

Das Geheimnis des Glücks ist die Freiheit, und das Geheimnis der Freiheit ist der Mut.

(Περικλῆς/ Perikles, *um 490 v. Chr. - 429 v. Chr.)

Table of contents

1 Introduction

1.1 Relevance of arterial function and arterio-ventricular interaction

In young healthy individuals, the large arteries are elastic. Normal aging is accompanied by progressive large arterial stiffening, which can be augmented by certain medical conditions such as obesity or diabetes. However, patients with certain types of congenital heart disease (CHD) or genetic disorders have increased arterial stiffness already at young age.

The Chinese philosopher Laozi (ca. 500 B.C.) stated more than 2000 years ago that elasticity is associated with youth and stiffness with death:

"Men are born soft and supple; dead they are stiff and hard. Plants are born tender and pliant; dead, they are brittle and dry. Thus whoever is stiff and inflexible is a disciple of death. Whoever is soft and yielding is a disciple of life. The hard and stiff will be broken. The soft and supple will prevail."

Laozi (ca. 500 B.C.)

Comparatively recently, cardiovascular (CV) researches have provided scientific evidence that increased arterial stiffness is indeed an independent risk factor for CV morbidity and mortality.(Vlachopoulos C *et al.*, 2010) Briefly, large arterial stiffening results in a lower diastolic blood pressure and diminished diastolic perfusion of the end-organs such as the heart, where adverse remodeling of the myocardium may eventually lead to heart failure with

preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF).(Borlaug BA *et al.*, 2007; Shim CY, 2011; Weber T and Chirinos JA, 2018; Chirinos JA *et al.*, 2019) The effect that arterial stiffening has on cardiac function is known as arterio-ventricular interaction. Adults hospitalized for HFrEF and HFpEF have 5-year mortality rates of approximately 75%.(Shah KS *et al.*, 2017)

Though there is evidence that several types of CHD, genetic connective tissue disorders or primarily non-cardiac systemic disorders are associated with increased arterial stiffness, the etiology, extent, physiologic impact, changes with age and prognostic implications of vascular changes in this context are not well understood to date. This may in part be attributed to the pathophysiologic heterogeneity and relative rarity of the conditions mentioned above, making it difficult to perform larger scale studies. However, it may at least in part also be the result of insufficient funding of adequate research.

1.2 Importance of arterial stiffness related research in children

Since 1985, the US National Institute of Health has spent over 565 million US$ for research projects related to arterial stiffness, with an exponential increase seen over the last few years (Figure 1a). Only a small fraction of this amount was spent on projects related to congenital CV risk factors, e.g. 2.3% on pediatric (Figure 1b) and 0.3% on CHD related studies (Figure 1c). Pediatric arterial stiffness research has been funded consistently over the last decade, even though at a low level with on average 1.2 million US$ per year. CHD related research on arterial stiffness, however, has received no National Institute of Health support for over a decade. Thus, even though arterial stiffness has been increasingly recognized as an important

research area in the general population, patients with CV risk factors since childhood have so far only received a minuscule “piece of the cake”.

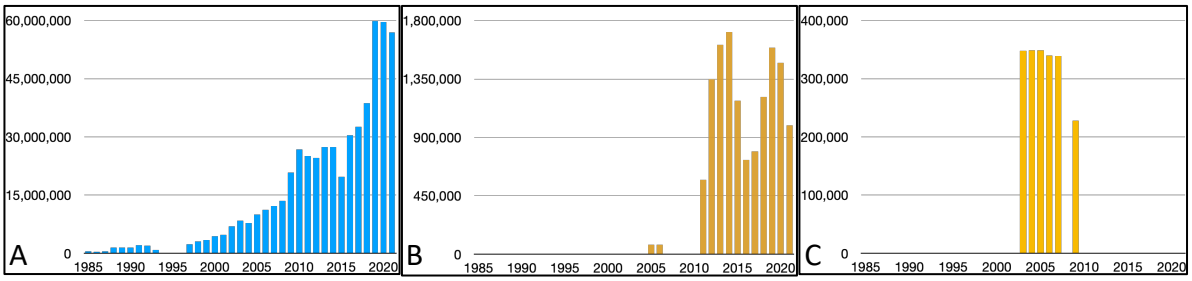

Figure 1: National Institute of Health funding on arterial stiffness between 1985 and 2021. The search was conducted using https://reporter.nih.gov using the following keywords in project title or abstract and excluding subprojects: A: arterial stiffness, B: arterial stiffness AND pediatric, C: arterial stiffness AND congenital heart disease. Project funding in US$ (y-axis; note the specific scale for each subfigure). Year of funding (x-axis).

This relative lack of funding corresponds to a relatively low research output and thus data on arterial stiffness in patients with CHD and/or CV risk factors acquired during childhood or adolescence. In fact, of all PubMed listed publications in the field of arterial stiffness, only 1.8% evaluated patients with CHD (Figure 2). The published data on non-CHD-related predisposing conditions for increased arterial stiffness is even more scarce (Figure 2).

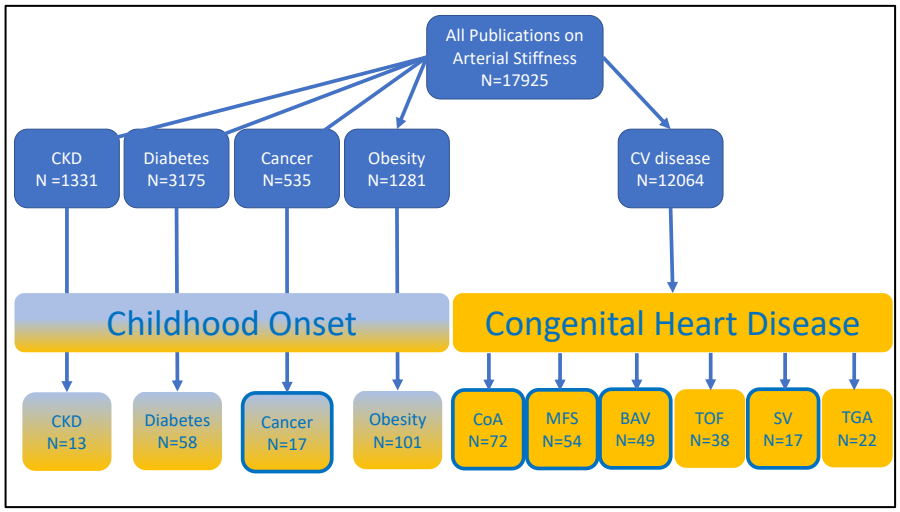

Figure 2: Number of articles (N) published on “arterial stiffness” in general and in combination with disease entities known to be associated with increased arterial stiffness. The search was conducted in March 2022 using PubMed (https://pubmed.ncbi.nlm.nih.gov). Blue-orange background represents childhood onset, orange background indicates pre-natal onset. Blue frame marks cardiovascular risk factors evaluated and presented herein. CV: cardiovascular; CKD: chronic kidney disease; CoA: Aortic coarctation; MFS: Marfan syndrome; BAV: bicuspid aortic valve; TOF: Tetralogy of Fallot; SV: single ventricle; TGA: transposition of the great

This paucity of data and funding contradicts the demographic changes that have been occurring over the past few decades. Improved treatment options for children with CHD as well as other pediatric diseases such as cancer, chronic kidney disease (CKD), or diabetes type 1 have led to an increasing number of children surviving well into adulthood.(Glinianaia SV *et al.*, 2020) Nearly 90% of Belgian children born with CHD between 1990 and 1992 have survived into adulthood.(Moons P *et al.*, 2010) Children with cancer have 5-year survival rates above 80% in high-income countries.(Lam CG *et al.*, 2019)

At the same time, the prevalence of obesity and even type 2 diabetes among youth has been high.(Chooi YC *et al.*, 2019) During the SARS-CoV2 pandemic, children and adolescents have been particularly affected by the necessary restrictions on social contacts imposed by many governments. Several studies have demonstrated a change in dietary habits towards unhealthy food choices and overall a decreased level of physical activity, resulting in weight gain during the pandemic.(Stavridou A *et al.*, 2021) As an example, during the SARS-CoV2 related lockdown in 2020, the prevalence of overweight and obesity among Chinese high school students has increased from 26.6% to 30.0%, and from 16 to 18.8%, respectively.(Yang S *et al.*, 2020) A longitudinal study from Cologne, Germany, has shown that primary school children have developed increasing body mass index (BMI) and BMI Z-score as well as diminished physical fitness and motor skills during the pandemic, particularly those with lower socioeconomic background.(Wessely S *et al.*, 2022) Whether these changes persist into adulthood and how they will impact the CV risk profile in the future, remains to be seen.

Naturally, etiology and extent of increased arterial stiffness in children with chronic diseases are quite heterogeneous. The unifying factor is that children will be exposed to the

adverse effects of increased arterial stiffness much longer than the average adult with arteriosclerotic CV disease. At this time we can only speculate how this will impact CV morbidity and our healthcare systems in the decades to come.

1.3 Study aim

It was the aim of the projects presented herein to gain a better understanding of the mechanisms underlying arterial dysfunction in patients with CHD or CV risk factors acquired early in life. We pursued this goal by using a multimodal approach that analyzed different aspects of arterial structure and function and interpreted these changes in relation to cardiac function and age. We hypothesized that the vascular phenotype depends on the underlying diagnosis and that arterial stiffness correlates with cardiac function and age. The types of patients analyzed herein were:

a) Coarctation of the aorta (CoA[$#]) and bicuspid aortic valve (BAV[#]), which are known to be associated with increased aortic stiffness,
b) Marfan syndrome (MFS[#]), which is mostly caused by mutations in the ubiquitously expressed extracellular matrix protein Fibrillin-1 and associated e.g. with aortic root aneurysms,
c) Single ventricle (SV[*]) patients with Fontan circulation, who are most vulnerable to changes in afterload, and
d) Childhood cancer survivors (CCS) following chemotherapy with cardiotoxic agents.

Funding agencies:
$ Swedish Heart-Lung Foundation (CGW)
# ALF (regional and national funding agency for clinical research; CGW)
* Swedish Children's Heart Foundation (CGW)

We even performed comparisons to coronary artery disease (CAD) patients, to help us understand mechanistic differences between congenital and acquired changes. Lastly, we generated a *Drosophila melanogaster* model for assessment of vascular and ventricular function which may facilitate pharmacological screening for agents treating arterial stiffening.

2. Background

2.1 Arterial characteristics and physiology

Arteries – from proximal to distal - can be categorized as 1. elastic arteries, 2. muscular arteries and 3. arterioles. Histologically, they consist of three layers, the endothelium, media and adventitia. The arterial system serves two purposes: a) as a conduit, transmitting blood with oxygen and nutrients to the periphery, and b) as an elastic buffer, converting pulsatile, high-pressure flow in the proximal aorta into low pressure, non-pulsatile flow in the capillary bed.(Ooi H *et al.*, 2008)

The elasticity of a vessel is determined by its distending pressure, wall structure (collagen, elastin, smooth muscle tone), and factors modulating vascular tone. Large elastic arteries have the highest elastin-collagen ratio in their medial layer. In young healthy individuals, the large arteries are elastic and exhibit a cushioning effect ("Windkessel effect") on the pulsatile flow. The cushioning effect of the large arteries gradually converts the pulsatile flow generated by left ventricular (LV) contraction to an almost continuous flow in the microvasculature. If the "Windkessel effect" functions optimally, the arterial pulse wave

is reflected distally and returns to the heart in diastole, thereby augmenting diastolic coronary artery perfusion and reducing cardiac afterload (Figure 3). Other organs such as the kidney, brain or placenta (and thereby the unborn child) also benefit from stable flow and pressure throughout the cardiac cycle.(Safar ME *et al.*, 2003; Tomiyama H and Yamashina A, 2010)

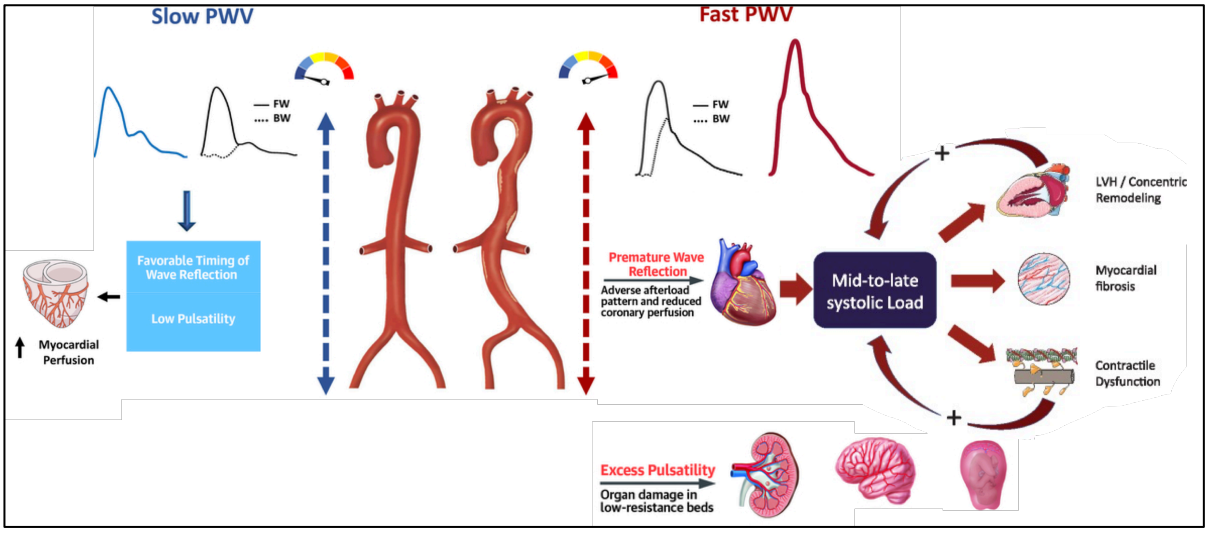

Figure 3: Role of large artery stiffness in health and disease In young healthy adults, a compliant aorta (left): (a) effectively buffers excess pulsatilty due to the intermittent left ventricular ejection; (b) exhibits a slow pulse wave velocity (PWV), which allows pulse wave reflections to arrive to the heart during diastole, increasing diastolic coronary perfusion pressure but not systolic ventricular load. A number of factors (aging, lifestyle, etc.) increase aortic wall stiffness, which leads to several adverse hemodynamic consequences. Aortic stiffening leads to increased forward wave amplitude on one hand, and premature arrival of wave reflections to the heart on the other. These hemodynamic changes result in adverse patterns of pulsatile load to the left ventricle in systole and a reduced coronary perfusion pressure in diastole, ultimately promoting myocardial remodeling, dysfunction, failure and a reduced perfusion reserve (even in the absence of epicardial coronary disease). This adverse hemodynamic pattern also results in excessive pulsatility in the aorta, which is transmitted preferentially to low-resistance vascular beds (such as the kidney, placenta and brain). PWV: pulse wave velocity; BP: blood pressure. **Modified and reproduced with permission from Weber and Chirinos, 2018 and Chirinos *et al., 2019*.**

Factors modulating vascular tone include endothelial-derived (e.g. nitric oxide (NO), endothelin-1), neurohumoral (e.g. acetyl choline, norepinephrin) and metabolic factors (e.g. pO2, pCO2). The endothelium, i.e. the inner lining of the vessel, is constituted of endothelial cells, which biosynthesize NO and other vasoactive substances which regulate vascular tone, hemostasis and permeability. Endothelial NO leads to vasodilation, and inhibits e.g. vascular

smooth muscle cell growth, platelet aggregation, and adhesion of leucocytes to endothelial cells, thereby exhibiting a protective effect against arteriosclerosis. (Simionescu M, 2007; Tomiyama H and Yamashina A, 2010)

2.2 Physiology of arterial stiffening and its effects on the heart

Arterial stiffness increases if any of the structural or functional factors determining arterial elasticity are disturbed. Structural changes include thickening of the intima-media with smooth muscle hypertrophy, increased content of collagen and glycosaminoglycans, calcification, and other changes in extracellular matrix (congenital or acquired).(Et-Taouil K *et al.*, 2003; Ooi H *et al.*, 2008) Functional changes include endothelial dysfunction, altered endothelial permeability due to structural changes, and abnormal vasoconstrictor responses. With damage of the endothelial layer, e.g. in atherosclerosis or inflammation, endothelial function is reduced and thereby the vessels ability to dilate is impaired.

Stiffer large arteries are associated with a loss of the Windkessel effect, i.e. the pulse wave travels faster, is reflected earlier (i.e., in late systole instead of in diastole), and the microvasculature is exposed to a higher pulsatile load. Consequently, central systolic pressure (CSP) increases ("isolated systolic hypertension"), central diastolic pressure decreases, and the pulse pressure is amplified (Figure 3). Diminished diastolic pressure results in diminished diastolic perfusion of the end-organs. In the heart, this impairs coronary perfusion, and increases the risk for subendocardial ischemia which in turn will impair myocardial relaxation.(Borlaug BA *et al.*, 2007; Shim CY, 2011) In addition, a higher end-systolic pressure affects myocardial thick-thin myofilament interactions and crossbridge dissociation, which

also affects myocardial relaxation.(Borlaug BA *et al.*, 2007) The effect that arterial stiffening has on cardiac function is known as arterio-ventricular interaction.(Westerhof N and O'Rourke MF, 1995) Gradually, adverse remodeling which may include myocardial hypertrophy, fibrosis, diastolic and/or systolic dysfunction (Figure 3). Eventually this may lead to heart failure with HFpEF or HFrEF – both of which have 5-year mortality rates of 75% in adults hospitalized for heart failure.(Shah KS *et al.*, 2017; Weber T and Chirinos JA, 2018; Chirinos JA *et al.*, 2019) Unlike for HFrEF, treatment options for HFpEF remain limited. There is some data supporting the use of exercise therapy, stains, anakinra (interleukin 1 antagonist) and immunomodulatory drugs.(Plitt GD *et al.*, 2018)

Other organs such as the brain, retina, kidneys or placenta (and thereby the unborn child) can also be damaged through the increased pulsatile load and diminished diastolic perfusion pressure (Figure 3).(Vlachopoulos C *et al.*, 2015; Weber T and Chirinos JA, 2018; Chirinos JA *et al.*, 2019)

2.3 Conditions associated with arterial stiffening

Large arterial stiffening well-known predictor of cardiovascular morbidity and mortality in the general population.(Vlachopoulos C *et al.*, 2010) Normal aging is accompanied by progressive large arterial stiffening due to extracellular matrix changes (increasing collagen/elastin ratio, collagen/elastin disarray, calcification) and cellular mechanisms (endothelial cell dysfunction, vascular smooth muscle cell stiffness, and cell-matrix interactions).(Vatner SF *et al.*, 2021) Accelerated arterial aging has been extensively studied in adults with traditional CV risk factors such as e.g. hypertension, obesity, diabetes, hypercholesterolemia, smoking, or CKD.

The mechanisms involved are in part disease-specific and include neurohormonal activation of e.g. the renin-angiotensin-aldosterone and sympathetic nervous systems, as well as extracellular matrix changes, inflammation and calcification (Duprez DA, 2007; Aroor AR *et al.*, 2018; Lacolley P *et al.*, 2020; Nardone M *et al.*, 2020)

Genetic and epigenetic factors play a role as well.(Lacolley P *et al.*, 2020) Linkage and polymorphism studies have identified genes in several pathways as modulators of arterial stiffness. Examples include the renin–angiotensin–aldosterone system, elastic fiber structural components, matrix metalloproteinases, the NO pathway, inflammatory molecules, beta-adrenergic and endothelin receptors.(Lacolley P *et al.*, 2009; Lacolley P *et al.*, 2017)

2.4 Arterial stiffness and arterio-ventricular interaction in patients with congenital heart disease or cardiovascular risk factors acquired early in life

As CHDs are diverse, their associated arterial changes are anything but a “one size fits all”. What patients with arterial changes due to CHD, genetic disease or CV risk factors acquired early in life have in common is that they are exposed to increased arterial stiffness for a life time (or close to that) – as opposed to the typical patient with acquired CV disease (CVD).

The most well studied congenital diseases in the field of arterial stiffness are CoA, BAV, and MFS - all of which are associated with intrinsic aortic wall abnormalities that extend beyond the actual anatomic lesion of aortic dilation vs narrowing.(Isner JM *et al.*, 1987; Nataatmadja M *et al.*, 2003) Over the last few decades, it has become evident that these

histologic abnormalities cause increased arterial stiffness.(Hirata K *et al.*, 1991; de Divitiis M *et al.*, 2001; Tzemos N *et al.*, 2010; Humphrey JD and Tellides G, 2019)

There is a paucity of CHD specific data on arterial-ventricular interaction. While adults with MFS may have intrinsically impaired LV contractility, arterial-ventricular interaction has been suggested as a cause of diastolic LV dysfunction in adults with e.g. BAV or repaired CoA.(Lee SY *et al.*, 2015; Li VW and Cheung YF, 2015; Loeper F *et al.*, 2016) Regarding pediatric data, we have previously shown in children with well repaired CoA and no significant residual gradient across the site of repair, that there is a negative correlation between ascending aortic stiffness and diastolic function.(Lombardi KC *et al.*, 2013) However, we were unable to confirm such a correlation in 50 children with BAV even though both ascending aortic stiffness and diastolic function were both abnormal compared to controls.(Weismann CG *et al.*, 2016) These findings were the stepping stone for a more extensive multimodal assessment which is presented in this research report.

A group of CHD patients that may be particularly vulnerable to the effects of increased arterial stiffness are those with SV physiology following Fontan-type palliation with a total cavopulmonary connection (TCPC) who are prone to develop HFrEF and/or HFpEF and are at increased risk for premature cardiac mortality. Details on the many complications and management of Fontan patients can be found elsewhere.(Gewillig M, 2005; Rodriguez FH and Book WM, 2020) It has been shown that Fontan patients have increased arterial stiffness and endothelial dysfunction which is associated with lower aerobic capacity, physical activity and quality of life.(Jin SM *et al.*, 2007; Lambert E *et al.*, 2013; Myers KA *et al.*, 2013; Tomkiewicz-Pajak L *et al.*, 2014; Goldstein BH *et al.*, 2016). In addition, Fontan patients with reduced

cardiac index compared to those with preserved cardiac index, have higher afterload with similar ejection fraction (EF), but worse myocardial diastolic function, suggesting that HFpEF may be a major factor leading to decreased exercise performance in those patients.(Saiki H *et al.*, 2016) If vascular function determines functional performance through arterio-ventricular interaction, it may serve as a therapeutic target in an effort to ameliorate progressive functional decline observed in adolescent and young adult Fontan survivors.(Goldstein BH *et al.*, 2016)

Children with acquired CV risk factors will be exposed to arterial stiffening for close to a life-time. An example for the effect non-cardiac conditions and treatment thereof can have on the CV system, are CCS. Adult patients previously treated with radiation and/or chemotherapy suffer permanent arterial damage which has been associated with CV and cancer mortality.(Mozos I *et al.*, 2017; Parr SK *et al.*, 2021) Increased arterial stiffness has been described in CCS as well, though – to the best of our knowledge – a correlation with outcome has not been confirmed to date.(Krystal JI *et al.*, 2015; Arnold N *et al.*, 2021)

Focusing on children and young adults with classic acquired CV risk factors though, there is evidence that childhood obesity, hypertension, dyslipidemia, diabetes and tobacco use are associated with intermediate CVD markers (e.g. LV hypertrophy, vascular stiffness) in young adulthood (Table 1).(Falkner B and Gidding S, 2021) In addition, several studies have demonstrated that childhood obesity, hypertension, hyperlipidemia, tobacco exposure as well as low birth weight, psychosocial and socioeconomic factors all are associated with clinical CVD during adulthood.(Pool LR *et al.*, 2021)

Table 1: The relationship of risk factors in childhood to adult cardiovascular and metabolic outcomes. **Reproduced from (Falkner B and Gidding S, 2021)**

Table 1. The relationship of risk factors in childhood to adult cardiovascular and metabolic outcomes

Risk factor in childhood	Atherosclerois	Myocardial dysfunction	Type 2 diabetes	Cerebrovascular disease	Vascular stiffness/small vessel disease	Chronic kidney disease
Hypertension	X	X	X	X	X	X
Elevated LDL-C	X			X	X	
Metabolic dyslipidemia	X		X	X	X	
Type 1 diabetes	X	X			X	X
Smoking	X	X			X	
Obesity	X	X	X	X	X	X
High sugar/high saturated fat diet	X		X			
Physical inactivity		X	X		X	

LDL-C, low-density lipoprotein cholesterol.

Thus, even though arterial stiffness predicts outcome in the general population including children with the classic CVD risk factors described above, the longitudinal changes of arterial stiffness with age in patients with CHD or early acquired CV risk factors such as cancer treatment remain poorly understood. Ultimately, longitudinal follow-up will be crucial in determining changes in arterial stiffness and diastolic function over time and in response to changes in medical management. Ideally, treating arterial stiffness would decrease the risk for HFpEF in the long run.

2.5 Pharmacological treatment of increased arterial stiffness

We know that arterial stiffening is an important predictor of CV morbidity and mortality. Medications that have been shown to reduce arterial stiffness most effectively are antagonizing the renin-angiotensin-aldosterone axis, which is probably due to their anti-fibrotic effect.(Boutouyrie P *et al.*, 2011) Other options are dihydropyridine type calcium channel blockers and vasodilating beta-blockers. Statins have also been implicated in reducing arterial stiffness, especially peripherally. Most recently, promising data on sodium-

glucose co-transporter 2 (SGLT2) inhibitors have been published, which are approved for the treatment of diabetes mellitus type 2 and obesity. SGLT2 inhibitors reduce arterial stiffness by improving endotelial function and reducing collagen content and inflammation.(Durante W *et al.*, 2021) What remains unuclear is whether treating arterial stiffness improves long-term outcome independent of the underlying condition.

3. Methods used to assess arterial function

There are several complementary methods available that help characterize arterial structure, stiffness and function at different levels non-invasively. The methods most relevant to the current study are described below.

3.1 Common carotid intima media thickness and roughness

Common carotid intima media thickness (cIMT) is a well-established and commonly used marker of (subclinical) arteriosclerosis in adults but also in children.(Lorenz MW *et al.*, 2007; El Jalbout R *et al.*, 2022) It is thought to reflect arterial health in general. The common carotid artery is easy to interrogate by ultrasound using standard equipment with a high-frequency linear array transducer. Along a 10-mm segment, semi-automated measurements of mean cIMT using commercial software (Figure 4). Pediatric reference data for cIMT as well as for cIMT/lumen dimension ratio are available.(Doyon A *et al.*, 2013; Semmler L *et al.*, 2021)

Carotid intima-media roughness (cIMR) has been shown to be to correlate with CV risk profile as well and may be a more sensitive marker for arteriosclerosis than cIMT.(Wu Y *et al.*, 2019; Wu Y *et al.*, 2019) For children, normative IMR data are available.(Dalla Pozza R *et al.*, 2016) In the same study, cIMR correlated positively with BMI Z-score and negatively with maximum oxygen uptake, a marker of physical fitness – supporting the notion that it may be a more sensitive marker for CV risk profiling than cIMT. However, its clinical utility is currently limited as it requires special software that is currently not commercially available.(Dalla Pozza R *et al.*, 2016)

Lastly, both, cIMT and cIMR are structural rather than a functional parameters. Thus, they are not suitable to evaluate short-mid-term treatment effects of e.g. pharmacologic interventions.

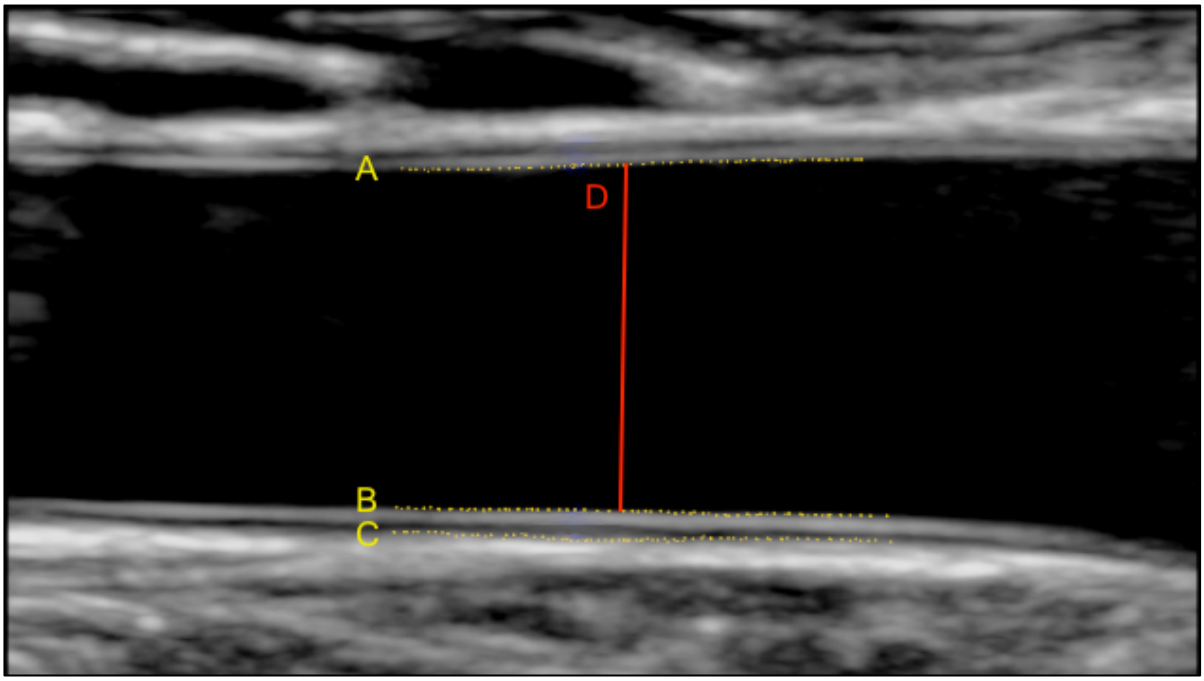

Figure 4: Illustration of common carotid artery measurements. Mean values for A, B, C were determined over a 1cm distance using the semiautomated software. D represents a single measurement. BC represents carotid intima media thickness; AB and D lumen dimension. **Reproduced from (Lindow A *et al.*, 2022)**

Focal arterial stiffness and distensibility can easily be assessed using ultrasound. Two-dimensional measurements of the ascending aorta or common carotid artery in peak systole and end-diastole can easily be obtained.(Stefanadis C *et al.*, 1990; Lombardi KC *et al.*, 2013; Weismann CG *et al.*, 2016) Based on these measurements, combined with systolic and diastolic blood pressure (BP), distensibility, stiffness, and strain can be calculated.(Stefanadis C *et al.*, 1990; Fahey M *et al.*, 2009; Lombardi KC *et al.*, 2013)

In a relatively large prospective Finnish study, carotid and aortic distensibility measurements have been associated with body mass index, BP, lipids and insulin resistance, suggesting that it may indeed be an early marker of acquired arteriosclerotic disease.(Mikola H *et al.*, 2017) We and others have demonstrated decreased ascending aortic distensibility in CHD patients (Vogt M *et al.*, 2005; Weismann CG *et al.*, 2021; Weismann CG *et al.*, 2021) Normal data on common carotid, ascending and abdominal aortic distensibility of approximately 400 children and adolescents aged 11-19 years have been published.(Hauser M *et al.*, 2013; Mikola H *et al.*, 2015) In addition, normative pediatric MRI data on aortic distensibility data are available on a cohort of 71 subjects.(Voges I *et al.*, 2012)

3.3 Pulse Wave Velocity

Aortic pulse wave velocity (PWV) is the most well-described independent predictor of CV events and widely considered the "gold standard" for measuring large arterial stiffness.(Laurent S *et al.*, 2006; Ben-Shlomo Y *et al.*, 2014) PWV describes the velocity of the forward pulse wave between two points and is calculated by dividing the distance between the two recording points by the time it takes for the pulse wave to travel the distance

(expressed in m/s; Figure 5). If the elasticity of the aorta is reduced, aortic stiffness is increased, and the Windkessel effect is attenuated. Thus, aortic PWV increases.

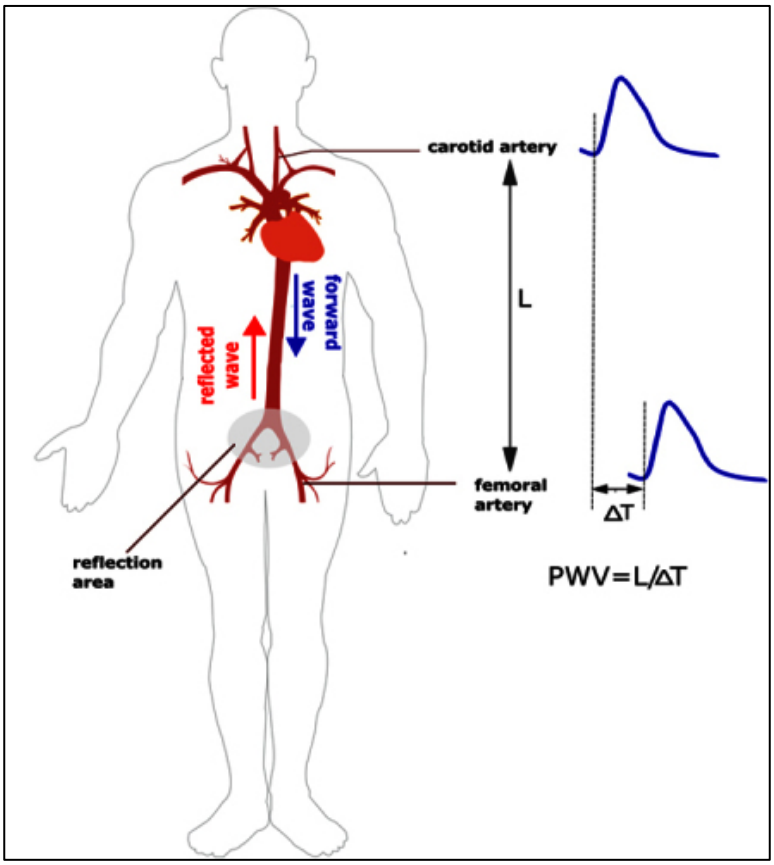

Figure 5: Determination of pulse wave velocity (PWV): PWV can be determined by dividing the distance between two points by the time (**Δ**T) it takes for the forward pulse wave to travel from the proximal to the distal point of measurement (L). Carotid-femoral PWV measurement is considered as a "gold standard" method. **Reproduced from (Jeroncic A *et al.*, 2016)**.

PWV is a direct measure of arterial stiffness that depends on age and BP, and is negatively related to height in adults.(Lee SY *et al.*, 2015; Qiu Q *et al.*, 2020) In terms of heart rate dependency, there are conflicting results: in elderly, pacing at higher heart rates results in increased PWV (possibly as there is less time for elastic recoil of the aorta during tachycardia), while no change in heart rate is seen when pacing younger adults.(Lantelme P *et al.*, 2002; Wilkinson IB *et al.*, 2002) In children who are still growing we are faced with

several confounding factors. With increasing age during childhood, height and BP increase and heart rate decreases. In a multivariate model though, age, height, and BP were found to be major positive predictors of PWV in children.(Reusz GS *et al.*, 2010) Normal PWV for children can be calculated as PWV [m/s] = 0.049 * age [years] + 0.008 * height [cm] + 0.0024 * MAP [mmHg] + 1.129.(Reusz GS *et al.*, 2010)

Several non-invasive methods and devices measuring PWV are currently on the market. These include the "gold standard" applanation tonometry (e.g. SphygmoCor®), piezoelectric mechanotransducers (e.g. Complior®) or single-cuff based oscillometry (e.g. Arteriograph®, MobilOGraph®).(Milan A *et al.*, 2019) Devices measuring carotid-femoral PWV (cfPWV) such as SphygmoCor® or Complior® have been shown to have high validity when compared to invasively measured aortic PWV.(Salvi P *et al.*, 2019) However, methods using a single cuff (e.g. Mobil-O-Graph®) produce PWV readings that are entirely dependent on age and BP.(Salvi P *et al.*, 2019) In addition, PWV can be measured by magnetic resonance imaging (MRI) or ultrasound – two methods that are mostly reserved for research purposes. MRI can measure local PWV in specific segments such as the aortic arch and descending aorta.

Normal data on large cohorts of adults, but also >1000 children and adolescents are available.(Collaboration TRVfAS, 2010; Reference Values for Arterial Stiffness C, 2010; Reusz GS *et al.*, 2010; Ben-Shlomo Y *et al.*, 2014; Vlachopoulos C *et al.*, 2015) While there is ample data on cfPWV as a risk factor for CV morbidity and mortality in the general population, one should be cautious when extrapolating to children and/or patients with CHD, particularly those with aortic pathology**.** First, the published normative pediatric data for PWV (using Arteriograph® and PulsePen®), were not invasively validated specifically in children.(Reusz GS

et al., 2010; Hidvegi EV *et al.*, 2012) This seems especially important for single cuff-based methods as the Arteriograph®. Another limitation of measuring cfPWV is that it detects only general stiffening along the pathway, but not focal changes as would be expected e.g. following aortic surgery.(Voges I *et al.*, 2016; Weismann CG *et al.*, 2021) Lastly, in the growing child, changes over time need to be interpreted with caution as growth in itself may affect PWV.

3.4 Central augmentation index and central blood pressure

Augmentation index (AIx) and central BP can be determined by pulse wave analysis of e.g. the brachial artery. While PWV describes the velocity of the forward pulse wave, the AIx is a marker of wave reflection. As arteries branch and become smaller peripherally, resistance increases. Wave reflection occurs when there is an abrupt increase in resistance. This usually occurs at the point of transition to muscular arteries, but may occur proximal, e.g. in patients with BAV who have eccentric flow jets through the aortic valve that are directed towards the ascending aorta (see section 4.1.1).

AIx is defined as the augmented pressure (i.e. difference in pulse height between forward and reflected wave) divided by the pulse pressure (Figure 6). During incremental pacing, an inverse linear relationship between AIx and heart rate has been demonstrated.(Wilkinson IB *et al.*, 2000) This is why AIx is commonly normalized to a heart rate of 75/min (Aix75). Other positive determinants of AIx are age, female sex, less height, and systolic BP.(Janner JH *et al.*, 2010, 2012)

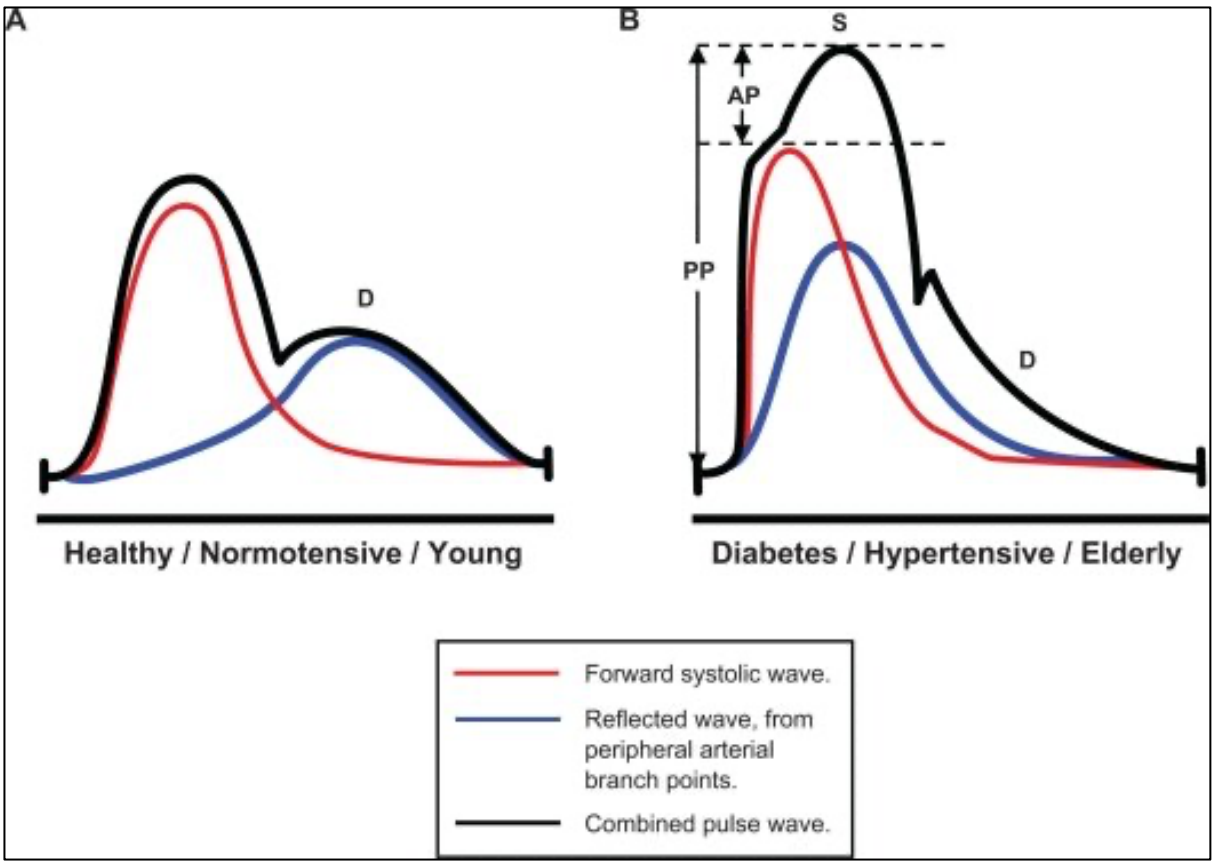

Figure 6: Schematic of arterial pressure waveforms and calculation of augmentation index (AIx), which is defined as the augmentation pressure (AP) divided by the pulse pressure (PP). **A)** Pulse waveforms in healthy compliant vasculature, timing of rebound wave reflection occurs during diastole (D). **B)** Pulse wave reflection is faster and earlier in stiffer arteries, thus amplifying the measured systolic blood pressure peak (S), and reducing diastolic pressures (D), hence PP is increased. **Reproduced from (Kum F and Karalliedde J, 2010)**.

In young healthy subjects, the forward wave is reflected fairly distal and returns to the heart in diastole, thereby augmenting coronary artery perfusion. The AIx in that case is negative or close to zero. With age or other CV risk factors associated with arterial stiffening (see section 2.3, 2.4), one loses much of the Windkessel effect, so the aortic PWV and wave reflection increase. The CSP, which is the sum of the forward and reflected wave, increases.

For adults, reference values are available for both central BP and AIx. (Janner JH *et al.*, 2010; Herbert A *et al.*, 2014) Pediatric reference values for AIx75 using the Mobil-O-Graph have been published for a small cohort of 134 patients. (Santos LMD *et al.*, 2021)

3.5 Digital pulse wave analysis

The pulse wave can also be analyzed more peripherally, e.g. in the index finger. One example is the EndoPAT® (see section 3.7) which measures the peripheral AIx in the index finger. Peripheral AIx is defined as the difference between the backward reflected peak (P2) and the systolic peak (P1) divided by P1 (peripheral AIx=(P2-P1)/P1). It is provided with and without correction for heart rate. In spite of technical and mathematical differences between peripheral and central AIx, they have previously been shown to correlate strongly with each other.(Munir S *et al.*, 2008)

Digital pulse wave analysis with photoplethysmography (Meridian Digital Pulse Analyzer®) is a quick and non-invasive method that analyzes the digital wave form to draw conclusions on micro- and macrovascular stiffness.(Millasseau SC *et al.*, 2006; Elgendi M, 2012; von Wowern E *et al.*, 2015) It has been validated much less extensively than for example the SphygmoCor® applanation tonometer, but is able to discriminate between patients with low, medium, and high CV risk profile.(Clarenbach CF *et al.*, 2012) Due to its short acquisition time of 70 seconds it may be particularly suitable in the pediatric population where cooperation is often a limiting factor. A number of variables and ratios that characterize small and large artery compliance as well as an 'aging index' are generated by the device (Figure 7). For detailed explanations and references regarding this methodology, please refer to von Wowern *et al.* (2015). (von Wowern E *et al.*, 2015)

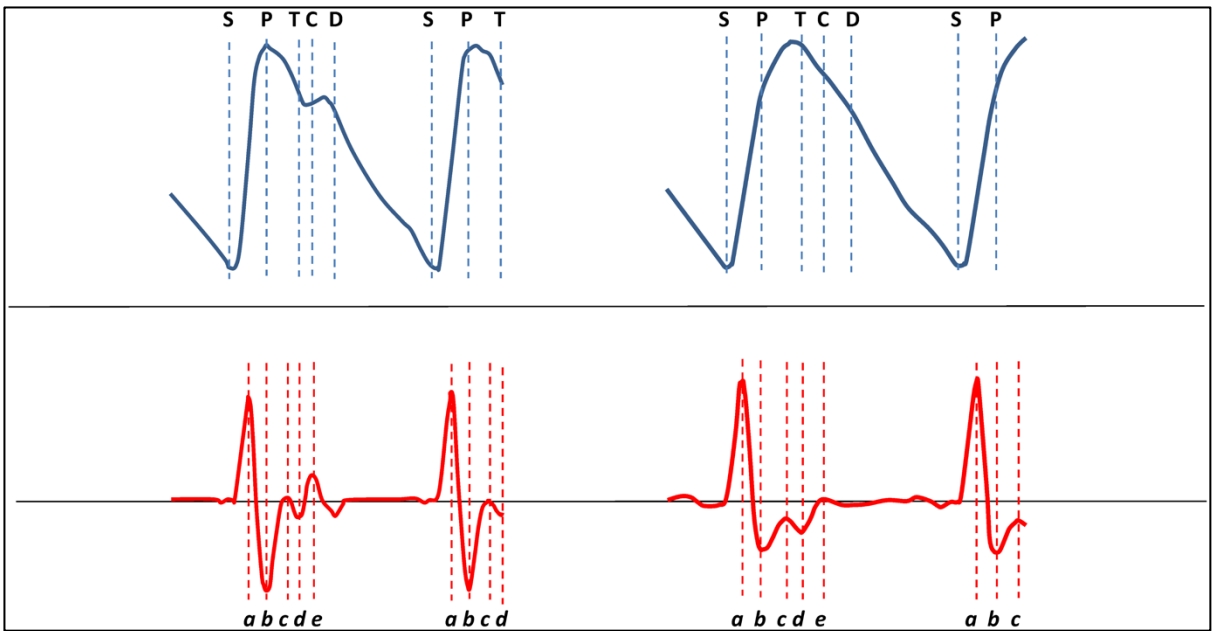

Figure 7: Digital photoplethysmograms and acceleration photoplethysmograms. Authentic digital photoplethysmograms (upper panels) of a 33-year old healthy woman (left panel, heart rate 65 bpm, aging index -0.87) and a 66-year old healthy man (right panel, heart rate 61, aging index -0.09). S = starting point of systole; P = peak of percussion wave; T = tidal wave; C = incisura wave; D = dicrotic wave. Note the absence of a distinct incisura and dicrotic notch in the right plethysmogram, and differences in negative amplitudes of b and d peaks in the acceleration plethysmograms (lower panels). The aging index is calculated as (b-c-d-e)/a. Aging index correlates positively with age. **Reproduced from (von Wowern E *et al.*, 2015)**.

3.6 Assessment of the microcirculation by laser Doppler

Large arterial disease leads to increased pulsatile load on the microvasculature and damage of organs such as the brain, heart, retina and kidneys. (Vlachopoulos C *et al.*, 2015) This may result in adverse remodeling with an increased intima-media/lumen ratio in the microcirculation. (Muiesan ML *et al.*, 2013)

Laser Doppler flowmetry (Perimed AB, Sweden) assesses cutaneous microvascular vasomotor function.(Morris SJ and Shore AC, 1996; Norman M and Martin H, 2003) Cutaneous blood flow is measured e.g. on the volar side of the forearm at baseline and in response to transdermal iontophoresis of endothelium-dependent (acetylcholine) and -independent

(sodium nitroprusside) agonists (Figure 8). (Odermarsky M *et al.*, 2007; Fernlund E *et al.*, 2015) The change of flow in response to those vasodilatory agents is measured using the same laser Doppler probe. Alternatively, neurally mediated and NO-dependent vasodilation due to local warming can be assessed. (Hodges GJ and Sparks PA, 2013, 2014)

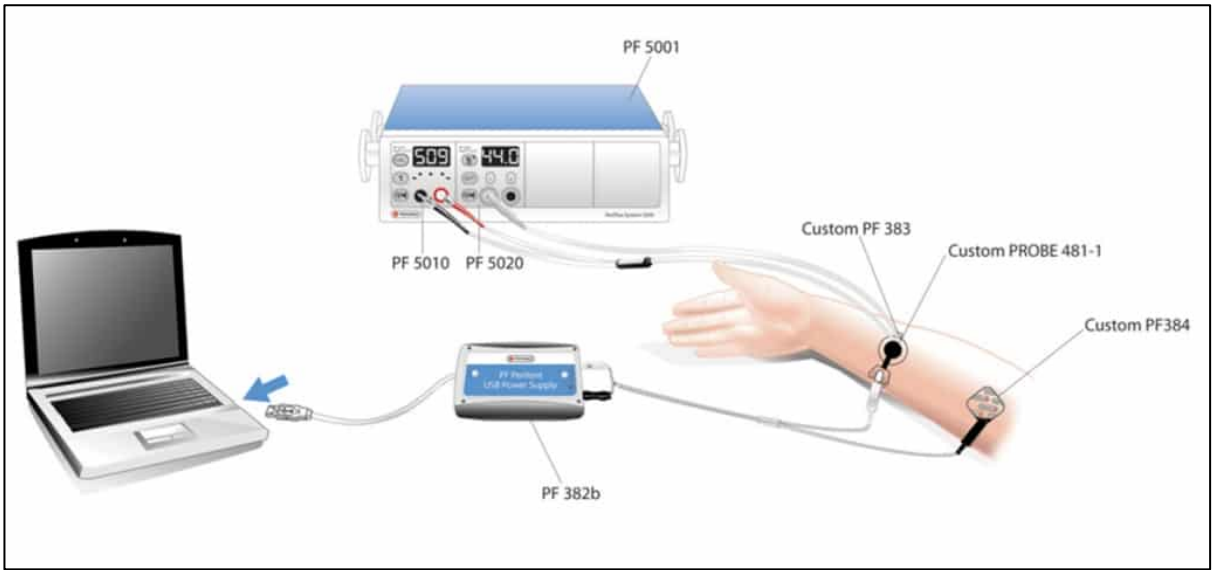

Figure 8: Schematic drawing of the experimental setup of a PeriFlux5000® connected to an iontophoresis laser Doppler probe. Iontophoresis can transport charged molecules or drugs into the skin by applying a small electrical charge. Combined with the laser Doppler, iontophoresis is a valuable tool for distinguishing between endothelium dependent and endothelium independent vsodilatory responses. **Reproduced from https://www.perimed-instruments.com.**

Laser Doppler with iontophoresis as described above can distinguished reliably between disturbed endothelium-depedent vs. endothelim-independent vasodilation. Most recently, this methodology identified impaired endothelium-dependent vasodilation in critically ill patients with SARS-CoV2, but not in controls with bacterial pneumonia. (Raia L *et al.*, 2022)

3.7 Endothelial function

Endothelial function is disturbed in patients with CAD, or CV risk factors such as diabetes mellitus, hypertension, obesity, renal failure, hypercholesterolemia, smoking and aging.(Lian BQ and Keaney JF, Jr., 2010) It is thought to be an early marker of CVD and predicts major CV events as well as mortality. (Axtell AL *et al.*, 2010)

Endothelial function can be assessed non-invasively by evaluating the hyperemia response following a few minutes of cuff occlusion of one arm. Flow mediated vasodilation (FMD) and EndoPAT® (Itamar Medical, Israel) are the most widely used methods.

With FMD, the shear-stress induced NO-dependent relative brachial artery dilation following distal cuff release is measured by ultrasound. A major methodological shortcoming of FMD is that its reliability is operator-dependent.

EndoPAT® (Itamar Medical, Israel), by contrast, evaluates the reactive hyperemia response in the index finger following proximal cuff occlusion (Figure 9). Peripheral arterial tone (PAT®) measures changes in pressure at the fingertip of both hands - rather than vasodilation like FMD. Hypoxia induced dilation of the microvasculature decreases resistance distally, leading to a hyperemic surge of blood to reperfuse the limb. This reaction is thought to be driven by both endothelium-dependent and -independent mechanisms. (Rosenberry R and Nelson MD, 2020)

Figure 9: Image of experimental set-up for the measurement of endothelial function using EndoPAT®. On the laptop screen, results of a typical completed examination are seen. The amplitude of the plethysmographic pulse curve (PAT® signal) is measured in both index finger tips for 5 minutes at baseline first. Then, the blood pressure cuff on one arm is inflated above the systolic blood pressure, so that the brachial artery is occluded for a 5 minute period, resulting in transient ischemia of that arm and a zero amplitude of the PAT® signal (lower panel of screen). During that period the PAT® signal in the contralateral arm is being monitored as well (upper panel of screen). Then, the cuff pressure is released rapidly, resulting in a sudden increase in PAT® in that arm, while the contralateral arm's signal remains unchanged. Reactive hyperemia index (RHI) is calculated by dividing post- to pre-occlusion PAT® signal ratio in the occluded side normalized to the control side. **Reproduced from www.itamar-medical.com.**

The reactive hyperemia index (RHI) is defined as the post- to pre-occlusion PAT® signal ratio in the occluded side normalized to the control side and baseline vascular tone. An RHI >1.67 is consistent with normal endothelial function in adults. As mentioned above, EndoPAT® has been validated extensively in adults with CV risk factors or manifest CVD and correlates with FMD. The advantage is that EndoPAT®, is observer-independent and highly reproducible even in children. (Hamburg NM *et al.*, 2008; Selamet Tierney ES *et al.*, 2009; Rubinshtein R *et al.*, 2010; Bruyndonckx L *et al.*, 2013)

4. Results

The following publications are included in this thesis and are listed below in chronological order, beginning with the most recent publication:

4.1 Multimodal assessment of vascular and ventricular function

4.1.1 Vascular and ventricular function in patients with left sided congenital heart disease

1. **Weismann CG**, Ljungberg S, Åkesson A, Hlebowicz J. Multimodal assessment of vascular and ventricular function in children and adults with bicuspid aortic valve disease. Front Cardiovasc Med. 2021 Mar 23;8:643900. PMID: 33834044. *Impact factor 4.79*
2. **Weismann CG**, Maretic A, Grell BS, Åkesson A, Hlebowicz J, Liuba P. Multimodal assessment of vascular and ventricular function in children and adults with repaired aortic coarctation. Int J Cardiol 2021 Jan 15;323:47-53. PMID: 32889020. *Impact factor 4.164.*
3. **Weismann CG**, Lombardi KC, Grell BS, Northrup V, Sugeng L. Aortic stiffness and left ventricular diastolic function in children with well-functioning bicuspid aortic valves. Eur Heart J Cardiovasc Imaging 2016; 17:225-30. PMID: 26072912. *Impact factor 4.1*
4. Chamberland CR, Sugeng L, Abraham S, Li F, **Weismann CG**. Three-dimensional Evaluation of Aortic Annular Shape in Children with Bicuspid Aortic Valves With and Without Aortic Coarctation. Am J Card 2015; 116:1411-7. PMID: 26375172. *Impact factor 3.2*

5. Lombardi KC, Northrup V, McNamara RL, Sugeng L, **Weismann CG**. Aortic stiffness and diastolic function in children following early repair of aortic coarctation. Am J Card 2013; 112(11):1828-33. PMID: 24035164. *Impact factor 3.2*

Our initial work at Yale University was retrospective in nature.(Lombardi KC *et al.*, 2013; Chamberland CR *et al.*, 2015; Weismann CG *et al.*, 2016) We showed that children and adolescents following CoA repair at a very young age as well as children with well-functioning BAV have abnormal LV diastolic function and aortic elasticity. While we found a correlation between ascending aortic elasticity and diastolic cardiac function in patients with a history of well-repaired CoA without a significant residual or recurrent gradient across the site of repair, this was not present in patients with isolated BAV. (Lombardi KC *et al.*, 2013; Weismann CG *et al.*, 2016) In addition, ascending aortic stiffening in BAV was first apparent in the age group of >8 years. We also evaluated the aortic valve annular eccentricity in children with BAV and/or CoA (with and without BAV) using 3-dimensional echocardiography and found that both groups had an elliptical shaped aortic valve annulus.(Chamberland CR *et al.*, 2015) We suggested that considering aortic valve annular eccentricity when balloon sizing the annulus before valvuloplasty may help improve interventional results in some patients.

To better understand the extent and mechanisms of above findings, we conducted a prospective study at the Pediatric Heart Center in Lund, Skånes University Hospital, Lund University, Sweden.(Weismann CG *et al.*, 2021; Weismann CG *et al.*, 2021; Weismann CG *et al.*, 2022) The patients studied were children and adults age 8 years and older. Study participants were recruited through the Swedish Registry for CHD (SWEDCON) and through advertisement. Patients with more than moderate residual stenoses or valvar insufficiencies

as well as associated complex CHD were excluded. We used a multimodal approach to characterize different aspects of the arterial system in combination with comprehensive echocardiograms to assess cardiac morphology, diastolic and systolic function.

For patients with well-repaired CoA we found decreased ascending aortic distensibility as well as increased CSP, cIMT, central and peripheral AIx75, and aging index. AIx75 was significantly increased only in the CoA subgroup with BAV, suggesting that the eccentric flow jet leads to proximal wave reflection. CfPWV, RHI and microcirculation were not significantly different between CoA and control patients. Diastolic function measured by tissue Doppler imaging was impaired in the CoA group relative to controls, and systolic function was marginally reduced. Both diastolic function and age correlated moderate-strongly with arterial characteristics (Figures 10 and 11, Table 2).

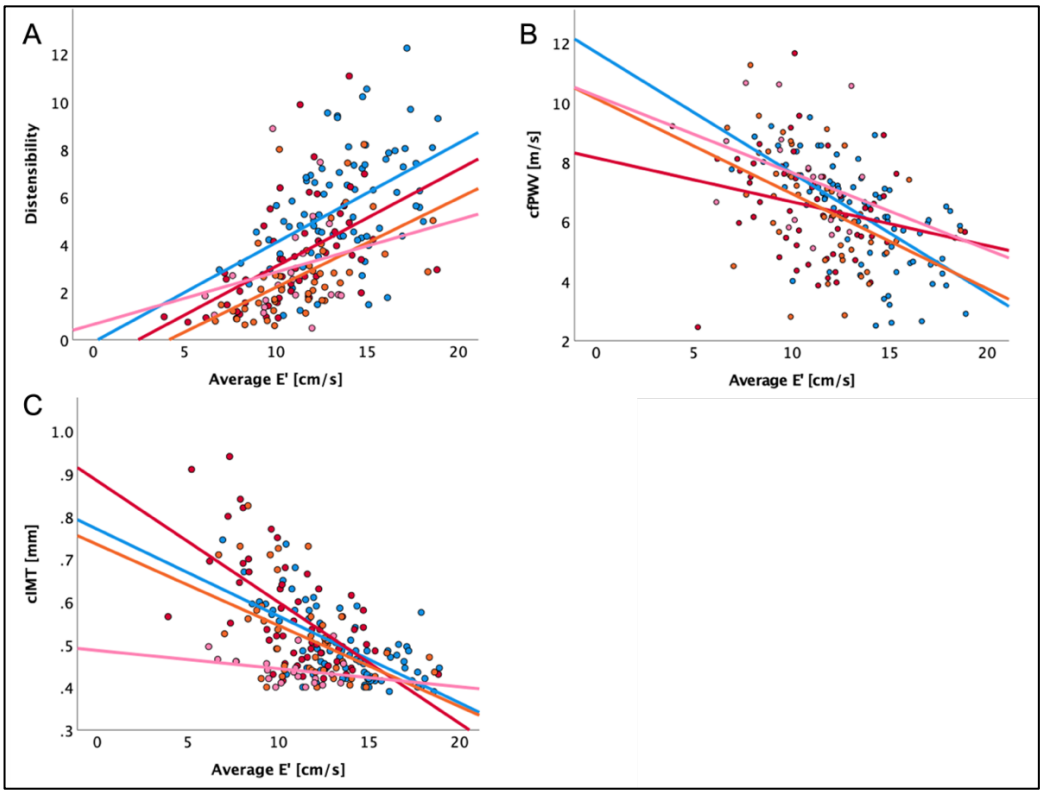

Figure 10: Scatter plot visualizing correlations between diastolic function (average E') and ascending aortic distensibility (**A**), carotid-femoral pulse wave velocity (cfPWV, **B**), and common carotid intima media thickness (cIMT, **C**) for controls (blue dots and regression line), patients with well repaired aortic coarctation (CoA; red dots and regression line), a history of bicuspid aortic valves (BAV, orange dots and regression line) and Marfan syndrome (MFS, pink dots and regression line).

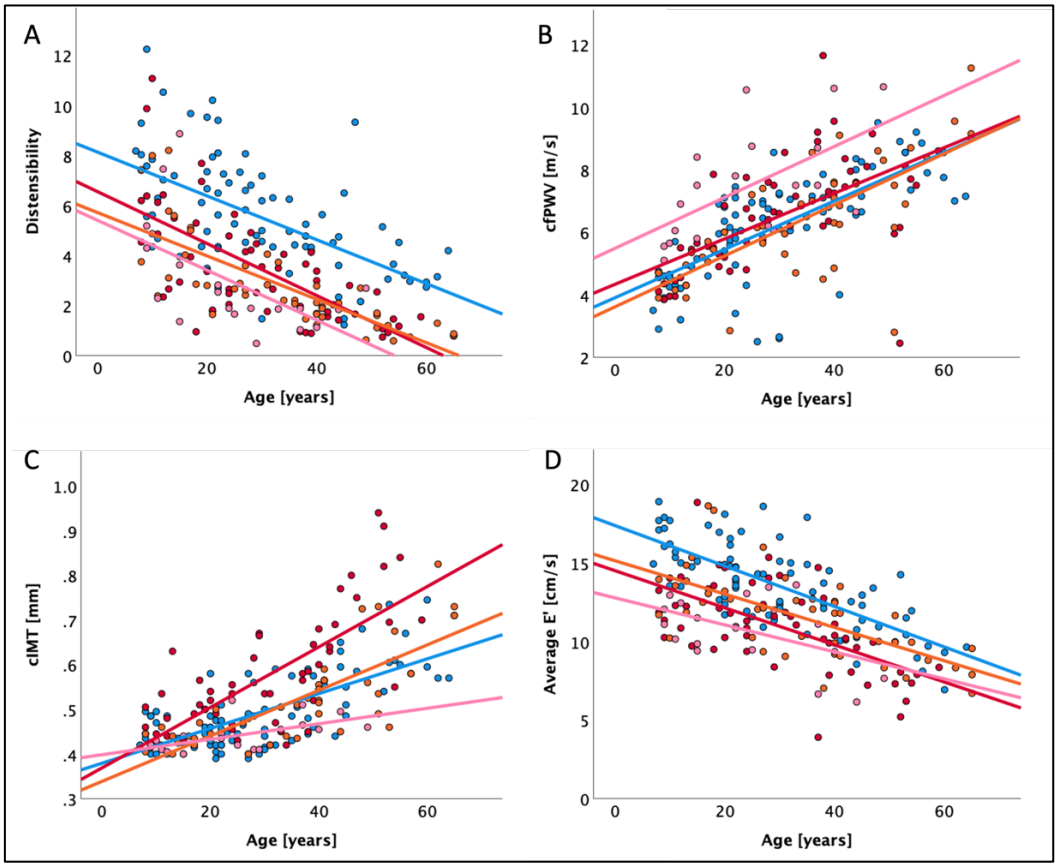

Figure 11: Scatter plot visualizing correlations between age and ascending aortic distensibility (**A**), carotid-femoral pulse wave velocity (cfPWV, **B**), common carotid intima media thickness (cIMT, **C**) and diastolic function (average E', **D**) for controls (blue dots and regression line), patients with well repaired aortic coarctation (CoA; red dots and regression line), a history of bicuspid aortic valves (BAV, orange dots and regression line) and Marfan syndrome (MFS, pink dots and regression line).

Table 2: Correlations between age or average E' (diastolic function) and cardiovascular characteristics per group. Pearson's correlation coefficient r and p-values are listed. A p-value <0.05 was considered statistically significant. CoA: coarctation of the aorta; BAV: bicuspid aortic valve; MFS: Marfan

		Controls (n=81)		CoA (n=56)		BAV (n=47)		MFS (n=20)	
		r	p	r	p	r	p	r	p
Age	**Distensibility**	-0.58	<0.001	-0.67	<0.001	-0.77	<0.001	-0.57	0.008
	IMT	0.71	<0.001	0.75	<0.001	0.79	<0.001	0.61	0.005
	PWV	0.71	<0.001	0.6	<0.001	0.72	<0.001	0.59	0.006
	E'	-0.73	<0.001	-0.61	<0.001	-0.66	<0.001	-0.50	0.024
E'	**Distensibility**	0.48	<0.001	0.50	<0.001	0.54	<0.001		N.S.
	IMT	-0.65	<0.001	-0.61	<0.001	-0.48	<0.001		N.S.
	PWV	-0.64	<0.001		N.S.	-0.46	<0.001		N.S.

In BAV patients (including those with prior intervention or valve replacement) ascending aortic stiffness, pulse wave reflection (central and peripheral AIx75, and aging index) and CSP were significantly increased, but cfPWV and endothelial function were not significantly different from controls. While these findings were similar to those in the CoA cohort, cIMT was not different from controls in BAV patients. In addition, diastolic function was only marginally reduced and systolic function was similar to controls. Overall, all parameters of arterial stiffness had moderate-strong correlations with diastolic dysfunction and age (Figures 10 and 11, Table 2). In the BAV group, ascending aortic distensibility, corresponding inversely to aortic stiffness, and had the strongest correlation with diastolic dysfunction, suggesting that the part of the arterial tree closest to the heart has the strongest effect on cardiac function. We concluded that that BAV is associated with increased proximal arterial stiffness and wave reflection, while other parameters associated with acquired CVD, namely cIMT, cfPWV, RHI, are normal, suggesting that the mechanism of arterial and cardiac stiffening is different from patients with acquired CVD.

4.1.2 Vascular and ventricular function in patients with Marfan syndrome

6. **Weismann CG**, Hlebowicz J, Åkesson A, Liuba P, Hanseus K. Comprehensive characterization of arterial and cardiac function in Marfan Syndrome - can biomarkers help improve outcome? Front Physiol. Accepted March 14, 2022. *Impact factor 4.134*

MFS is an autosomal-dominant connective tissue disorder, most commonly caused by missense mutations in the *Fibrillin 1* gene. MFS in adults and even children has been associated with increased aortic stiffness and LV diastolic but also systolic dysfunction. The

latter may be due to the underlying genotype and/or secondary to aortic stiffening (vascular-ventricular interaction). The aim of this study was to characterize arterial and cardiac function in MFS using a multimodal approach, including a biomarker panel.

We included 20 patients with MFS and 67 controls. Ascending aortic distensibility, cIMT and RHI were decreased, while all parameters of arterial wave reflection, stiffness and Brain Natriuretic Peptide (BNP) levels were increased in the MFS group. Both systolic and diastolic function were impaired relative to controls. Within the MFS group, no significant correlation between arterial and cardiac function was identified (Figures 10 and 11, Table 2). However, cfPWV correlated significantly with indexed LV mass and volume in MFS. BNP was the only biomarker significantly elevated in MFS following correction for age and sex.

Thus, MFS patients have generally increased aortic stiffness, endothelial dysfunction and measured BNP levels while cIMT is decreased, supporting that the mechanism of general stiffening is different from acquired vascular disease where cIMT is typically increased. CfPWV is associated with LV size, BP and plasma BNP levels in MFS patients. These may be early markers of disease progression that are suitable for monitoring pharmacological treatment effects in MFS patients.

4.1.3 Vascular and ventricular function in patients following Fontan palliation

7. Stalberg L, Grell BS, Hlebowicz J, Akesson A, Hanseus K, **Weismann CG**. Multimodal assessment of vascular function in patients with Fontan circulation. AEPC annual meeting, Sevilla, Spain, 17. Mai, 2019. Oral presentation.

In patients with SV physiology following palliation with a TCPC resulting in a "Fontan circulation", the pulmonary and systemic circuits are connected in series.(Gewillig M, 2005) Fontan patients are at risk for both HFpEF and/or HFrEF, particularly as they become adults. As there is no subpulmonary ventricle, the flow in the pulmonary circulation is non-pulsatile and depends on a low pulmonary vascular resistance as well as good diastolic function of the receiving single subsystemic ventricle. If diastolic cardiac function is impaired, filling of the systemic ventricle is reduced, resulting in reduced cardiac output and exercise performance even though the EF may be preserved. In adult Fontan patients with reduced diastolic function, arterial stiffness is also increased.(Chowdhury SM *et al.*, 2022) Our hypothesis was that vascular function is impaired in Fontan patients even at young age, and that increased arterial stiffness correlates with worse heart function.

Thirty-one Fontan patients and 52 matched controls were included in the study (Stalberg L *et al.*, 2019) Median age was 20 (IQR 12-22) years. There was no significant difference between the groups for age, sex, or height, but weight and BSA were significantly lower in the TCPC group. Following correction for age and sex, CSP and heart rate were significantly higher in the Fontan cohort, while there was no difference in brachial BP and central diastolic pressure. All parameters of arterial wave reflection, i.e. central and

peripheral AIx75 and aging index were significantly higher in patients versus controls (B= 22, 16 and 0.3 respectively, all p<0.001). However, there was no significant difference in cfPWV, cIMT, or RHI between groups. Regarding cardiac function, we found a decreased 4-dimensional EF (B=-14, p<0.001) and fractional area change (B=-5, p=0.006) of the systemic ventricle as well as diminished absolute global longitudinal strain, global circumferential strain, and diastolic function assessed by average medial and lateral systemic ventricle E' (B=3, 12 and 7, p<=0.002 for all). Due to the increased heart rate, which compensates for the diminished EF, cardiac index was comparable to controls. A subgroup analysis comparing patients with single right vs. LV morphology revealed no statistically significant differences between the two groups, though there was a trend towards lower fractional area change and EF in the systemic right ventricle group (p=0.068 and 0.095, respectively). Surprisingly, none of the vascular parameters correlated with systolic or diastolic cardiac function. Likewise, age correlated only with CSP, and cIMT, and negatively with diastolic function. This relative lack of findings is likely due to the heterogeneity of the different types of SV lesions and their associated aortic pathology and prior surgeries such as aortic arch reconstruction or CoA repair.

We concluded that Fontan patients have increased wave reflection and CSP, but no significant abnormalities in cIMT, general large artery stiffness, or endothelial function. Clinical management of TCPC patients should include monitoring and managing CSP.

4.1.4 Vascular and ventricular function in childhood cancer survivors

8. Characterization of Cardiac, Vascular and Metabolic Changes in Young Childhood Cancer Survivors. Broberg O, **Weismann CG**, Øra I, Wiebe T, Liuba P. Front Pediatr 2021 Dec 8;9:764679. *Impact factor 3.418*

Heart failure is the most common non-cancerous causes of death in CCS, and is, at least in part, due to prior treatment with cardiotoxic anthracyclines and radiotherapy.(Mertens AC *et al.*, 2008; Kero AE *et al.*, 2015; Leerink JM *et al.*, 2020) CCS are also at increased risk for e.g. metabolic syndrome which may further increase their risk for CV morbidity and mortality.(Chueh HW and Yoo JH, 2017) It was our aim to characterize CV changes in young adult CCS, in order to eventually develop preventive monitoring and treatment strategies for this cohort at risk for acquired CVD.

Fifty-three young adult otherwise healthy CCS who were treated with anthracyclines during childhood and 53 matched controls were included in this cross-sectional study.(Broberg O *et al.*, 2021) CCS sub-group analyses were carried out based on childhood exposure to low or high anthracycline dose. CCA distensibility and endothelial function were both significantly lower in CCS compared to controls, while there was no difference in cIMT. Systolic function was significantly impaired only in the high anthracycline dose group and correlated negatively with duration since treatment, but diastolic function was reduced in both CCS subgroups. Further, there were abnormalities in lipid markers, Apolipoprotein-B and Apolipoprotein-B /Apoliprotein-A1 ratio.

We concluded that young asymptomatic CCS exhibit cardiac, vascular, lipid and apolipoprotein changes that could account for increased risk for CVD later in life. These findings emphasize the importance of cardiometabolic monitoring even in young CCS.

4.2 Carotid artery characteristics in patients with congenital vs acquired cardiovascular risk factors

9. Lindow A, Kennbäck C, Åkesson A, Nilsson PM, **Weismann CG**. Common carotid artery characteristics in patients with repaired aortic coarctation compared to other cardiovascular risk factors. Int J Cardiology Congenital Heart Disease, Volume 7, March 2022, 100319.

CIMT, a well-known risk factor for CV morbidity and mortality, has been shown to be increased in patients with CoA. However, data on mechanism and clinical relevance in this population are scarce. Our aim was to gain mechanistic insights into cIMT thickening of patients with repaired CoA by comparing their wall architecture to patients with CAD, other congenital heart diseases (oCHD), and healthy controls.

A total of 310 children and adults were included (CoA (n=58), oCHD (n=96), CAD (n=68) and healthy controls (n=88). CIMT and lumen dimension were determined using semiautomated analysis software. Linear regression analyses were performed correcting for relevant covariates. While patients with repaired CoA and CAD both had significantly increased cIMT and cIMT/lumen dimension ratios, lumen dimension was increased only in

CoA patients (Figure 12). Furthermore, patients with repaired CoA had decreased CCA stiffness. CCA characteristics in the oCHD group were not significantly different from controls.

This suggests that the mechanism of cIMT thickening in patients with repaired CoA may differ from CAD. While there is concentric remodeling in the latter, we see predominant eccentric remodeling in the CoA group, which could be due to increased flow as a result of compliance mismatch at the CoA repair site. We therefore suggest that the prognostic value of cIMT in post-CoA patients should be validated separately prior to using it to guide clinical management in this group.

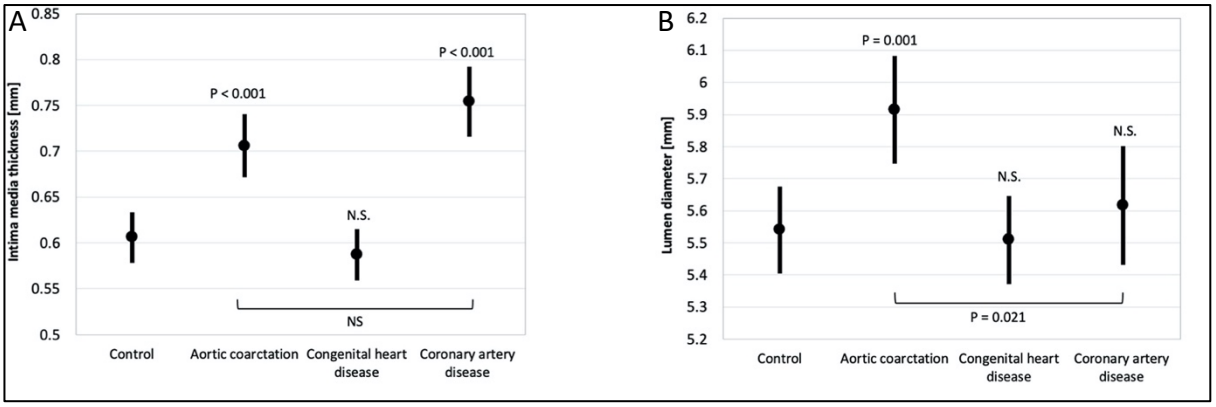

Figure 12: Common carotid intima media thickness (**A**) and lumen dimension (**B**) of patients with repaired aortic coarctation (CoA), other types of congenital heart disease (oCHD), coronary artery disease (CAD) and healthy controls following correction for age and sex. Data are derived from a Generalized Linear Model with Bonferroni correction and presented as estimated means (black filled circle) with 95% confidence interval (vertical line). Groups are compared to controls (p-value above the data points). In addition, CoA is compared to the CAD group (p-value below the data points). Reproduced from **(Lindow A *et al.*, 2022).**

4.3 Multimodal assessment of vascular and ventricular function in D. melanogaster

10. **Weismann CG**, Blice-Baum A, Tong T, Li J, Huang BK, Jonas SM, Cammarato A, Choma MA. Multi-modal and multiscale imaging approaches reveal novel cardiovascular pathophysiology in Drosophila melanogaster. Biology Open 2019 8: bio044339. PMID: 31455664. *Impact factor 1.962.*

In addition to the clinical studies described above, we established a novel, multi-modal and multiscale imaging approach for comprehensive assessment of CV physiology in *Drosophila melanogaster*.

Hdp(2) harbor a mutation in *wupA*, which encodes an ortholog of the human troponin I gene (*TNNI3*). *TNNI3* variants engender hypertrophic, restrictive or dilated cardiomyopathy in humans. We employed high-speed angiography, optical coherence tomography and confocal microscopy to reveal functional and structural abnormalities in the hdp(2) mutant, pre-pupal heart tube and aorta relative to controls. We demonstrated that the hdp(2) aortic and cardiac muscle walls are disrupted and that shorter sarcomeres are associated with smaller, stiffer aortas, which consequently result in increased flow and pulse wave velocities (Figure 13). The mutant hearts also displayed diastolic and latent systolic dysfunction. We concluded that hdp(2) pre-pupal hearts are exposed to increased afterload due to aortic hypoplasia. This may in turn contribute to diastolic and subtle systolic dysfunction via vascular-heart tube interaction, which describes the effect of the arterial loading system on cardiac function. Ultimately, the CV pathophysiology caused by a point mutation in a

sarcomeric protein demonstrates that complex and dynamic micro- and mesoscopic phenotypes can be mechanistically explained in a gene sequence- and molecular-specific manner. This model may facilitate larger scale pharmacological screening to ameliorate CV stiffening in the future.

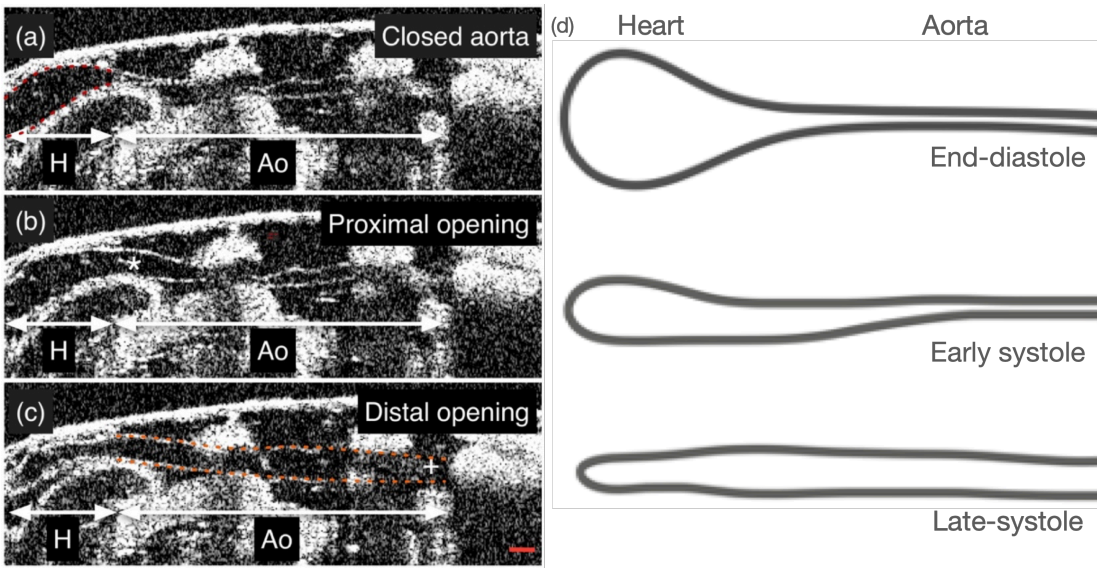

Figure 13: Optical coherence tomography based assessment of aortic pulse wave velocity. (**a**) The aorta is closed immediately prior to the initiation of cardiac systole. (**b**) The proximal (*) aorta opens shortly after the initiation of cardiac systole. (**c**) The distal (+) aorta opens some time (Δt) later. (**d**) Schematic representation of optical coherence tomography images shown on the left. Pulse wave velocity is given by PWV=Δx/Δt, where Δx is the distance between the proximal and distal aorta, and Δt is the time it takes for the pulse wave to travel Δx. H, heart; Ao, aorta. Red dashed line, cardiac wall; orange dashed line, aortic wall. Scale bar: 100 um. **Modified and reproduced from (Weismann CG *et al.*, 2019).**

5. Summary, clinical significance and future directions

In summary, we have shown that – depending on the underlying type of congenital heart defect, syndrome or risk factor acquired during childhood – different aspects of the arterial tree can be affected (Figures 14-18, Table 3).

5.1 Summary of findings by underlying congenital heart defect, syndrome or risk factors

5.1.1 Coarctation of the aorta

In patients following CoA repair without current evidence of re-CoA, we found diminished ascending aortic distensibility as well as increased cIMT, AIx, CSP and diastolic cardiac dysfunction compared to controls (Figure 14; Table 3). There were moderate-strong correlations between arterial characteristics and diastolic function as well as age. There was no evidence of general aortic stiffening though as cfPWV was not different from controls. Endothelial function and microcirculatory perfusion were normal as well.

These data suggest that the long-lasting effects of increased proximal arterial stiffness and early wave reflection in patients with well repaired CoA may contribute to diastolic function and HFpEF.

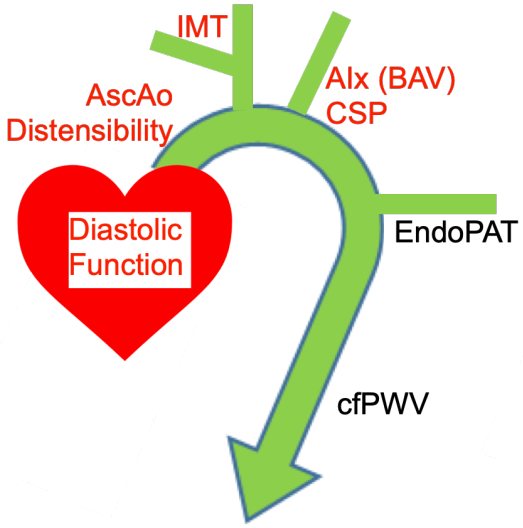

Figure 14: **Aortic coarctation**: Illustration of changes in arterial and cardiac characteristics in patients following repair of aortic coarctation compared to controls. Fonts are color coded: red – abnormal; black – no difference compared to controls. AscAo: ascending aortic; IMT: common carotid intima media thickness; AIx: augmentation index; BAV: bicuspid aortic valve; CSP: central systolic pressure; EndoPAT: endothelial function assessed by EndoPAT®; cfPWV: carotid-femoral pulse wave velocity.

5.1.2 Bicuspid aortic valve

In the BAV group, we also found diminished ascending aortic distensibility as well as increased AIx and CSP (Figure 15; Table 3). CIMT, endothelial function and cfPWV, however, were not different from controls. Diastolic function was only marginally decreased, but correlated nonetheless with parameters of arterial stiffness, esp. ascending aortic distensibility.

These data suggest that the long-lasting effects of increased proximal arterial stiffness and early wave reflection in patients with BAV may contribute to diastolic function and HFpEF. As the cIMT is normal, the mechanism of arterial and cardiac stiffening is different from patients with acquired heart diseases where cIMT is typically increased.

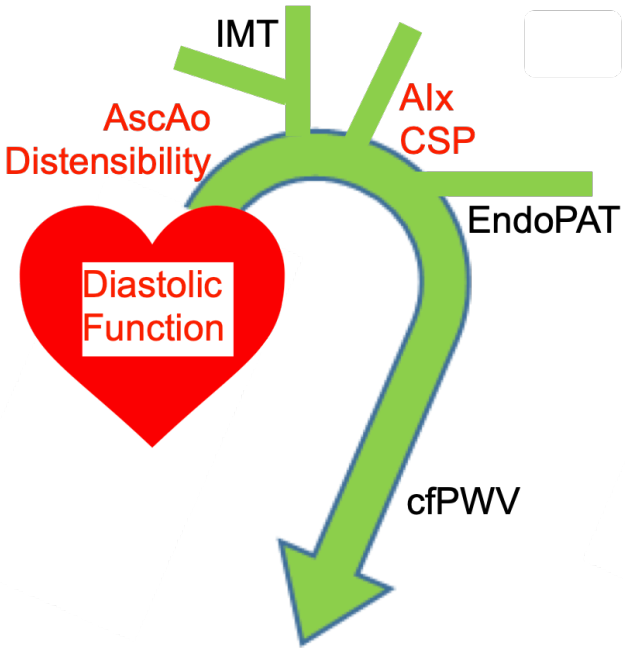

Figure 15: Bicuspid aortic valve: Illustration of changes in arterial and cardiac characteristics in bicuspid aortic valve patients compared to controls. Fonts are color coded: red – abnormal; black – no difference compared to controls. AscAo: ascending aortic; IMT: common carotid intima media thickness; AIx: augmentation index; CSP: central systolic pressure; EndoPAT: endothelial function assessed by EndoPAT®; cfPWV: carotid-femoral pulse wave velocity.

5.1.3 Marfan syndrome

In MFS, by contrast, we found not only increased ascending aortic distensibility and AIx, but also cfPWV (Figure 16; Table 3). These findings suggest general rather than focal aortic stiffening. In addition, there was evidence of endothelial dysfunction. Interestingly, cIMT was decreased compared to controls, which underscores that the etiology of arterial stiffening in this cohort is not related to atherosclerotic changes (where cIMT would be increased). In addition, systolic and diastolic cardiac function were diminished but did not correlate with arterial stiffness. However, cfPWV was associated with cardiac size, blood pressure and BNP levels.

These data suggest that cardiac dysfunction in MFS is not a direct result of arterial stiffening, but rather related to the underlying genotype. CfPWV and BNP levels may be early markers of disease progression that are suitable for monitoring medical treatment effects.

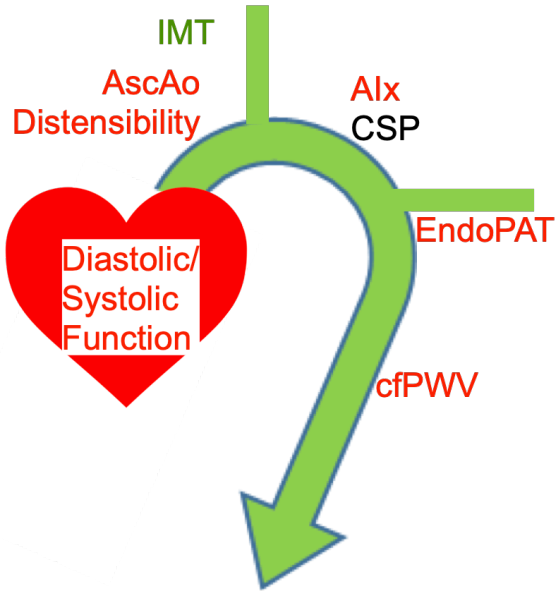

Figure 16: **Marfan syndrome**: Illustration of changes in arterial and cardiac characteristics in patients with Marfan syndrome compared to controls. Fonts are color coded: red – abnormal; black – no difference compared to controls; green – "better" than controls. AscAo: ascending aortic; IMT: common carotid intima media thickness; AIx: augmentation index; CSP: central systolic pressure; EndoPAT: endothelial function assessed by EndoPAT®; cfPWV: carotid-femoral pulse wave velocity.

5.1.4 Single ventricle physiology following Fontan palliation

In SV patients with Fontan circulation, we saw increased wave reflection (AIx) and CSP as well as significantly diminished systolic and diastolic cardiac function parameters (Figure 17; Table 3). However, there was no correlation between vascular and cardiac function, which may be due to the heterogeneity and small size of the cohort. In addition, carotid artery distensibility, cIMT, cfPWV and endothelial function were similar to controls though.

These data suggest that care should be taken to maintain a normal CSP in order to avoid additional stress on the SV circulation following Fontan-type palliation.

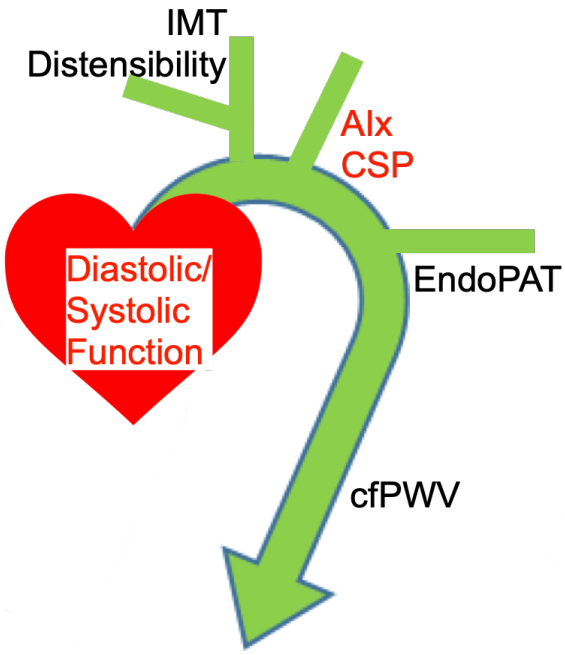

Figure 17: Single ventricle group following total cavopulmonary anastomosis: Illustration of changes in arterial and cardiac characteristics in single ventricle group following total cavopulmonary anastomosis compared to controls. Fonts are color coded: red – abnormal; black – no difference compared to controls. IMT: common carotid intima media thickness; AIx: augmentation index; CSP: central systolic pressure; EndoPAT: endothelial function assessed by EndoPAT®; cfPWV: carotid-femoral pulse wave velocity.

5.1.5 Childhood cancer survivors

CCS had impaired endothelial function and common carotid artery distensibility, but normal cIMT (Figure 18; Table 3). Central arterial dynamics were not assessed in this cohort. While systolic and diastolic function were significantly impaired, they did not correlate with arterial distensibility. However, time following cancer treatment was related to EF.

These data suggest that cardiotoxic chemotherapy affects not only the heart but also the arteries.

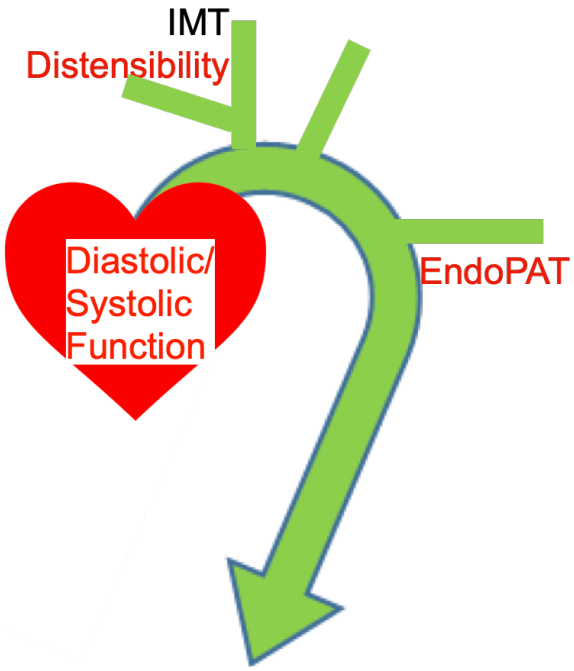

Figure 18: **Childhood cancer survivors**: Illustration of changes in arterial and cardiac characteristics in childhood cancer survivors compared to controls. Fonts are color coded: red – abnormal; black – no difference compared to controls. IMT: common carotid intima media thickness; AIx: augmentation index; CSP: central systolic pressure; EndoPAT: endothelial function assessed by EndoPAT®; cfPWV: carotid-femoral pulse wave velocity.

Table 3: **Summary of study findings by methodology and patient group**. The direction of the arrows indicates significant increase and decrease of each variable, compared to controls. The color coding indicates abnormal (red) vs. "better" than normal (green) . Fields with a blank background represent variables that were not different from controls in that patient group. The dark grey shading indicates variables that were not assessed in the respective cohort.

	Distensi-bility	AIx	cfPWV	cIMT	EndoPAT	Diastolic function	Ejection fraction
Aortic coarctation	↓	↑		↑		↓	
Bicuspid aortic valve	↓	↑				↓	
Marfan syndrome	↓	↑	↑	↓	↓	↓	↓
Single ventricle (Fontan)	*	↑				↓	↓
Childhood cancer survivors	↓*				↓	↓	↓

* Distensibility of the common carotid artery instead of the ascending aorta.
AIx: augmentation index; cfPWV: carotid-femoral pulse wave velocity; cIMT: common carotid intima media thickness; EndoPAT: endothelial function assessed by EndoPAT®.

5.2 Summary and interpretation of findings in the clinical context

While a correlation between arterial stiffness and diastolic cardiac function could be demonstrated for CoA and BAV, this was not evident in MFS, TCPC and CCS, suggesting that factors that directly affect both arteries and heart (i.e. *Fibrillin 1* mutation, complex structural changes, cardiotoxic drugs, respectively) may predominate in the latter groups.

Normal changes of arterial characteristics with age were best characterized by cIMT and cfPWV in controls and patients alike.

Increased arterial wave reflection appears to be associated with BAV, independent of the presence or absence of a CoA. This is likely due to the eccentric flow through the BAV, leading to proximal wave reflection.

Lastly, we were able to show that carotid artery remodeling in patients with repaired CoA is eccentric rather than concentric as seen in adults with CAD. Thus, we advise caution when interpreting vascular parameters in patients with congenital CV risk factors in the context of outcome data that is based on adults with classic acquired CV risk factors.

5.2 Future directions

Generally speaking, arterial stiffness in CHD can be categorized into three groups, which may overlap (Figure 19):

1. Intrinsic
2. Iatrogenic
3. Acquired

E.g. a patient who underwent late initial intervention for CoA may have intrinsically increased proximal aortic stiffness in addition to iatrogenic factors (e.g. surgical anastomosis, stent) and acquired changes due to long standing hypertension. A patient with MFS, by contrast, would be expected to have predominantly intrinsic changes.

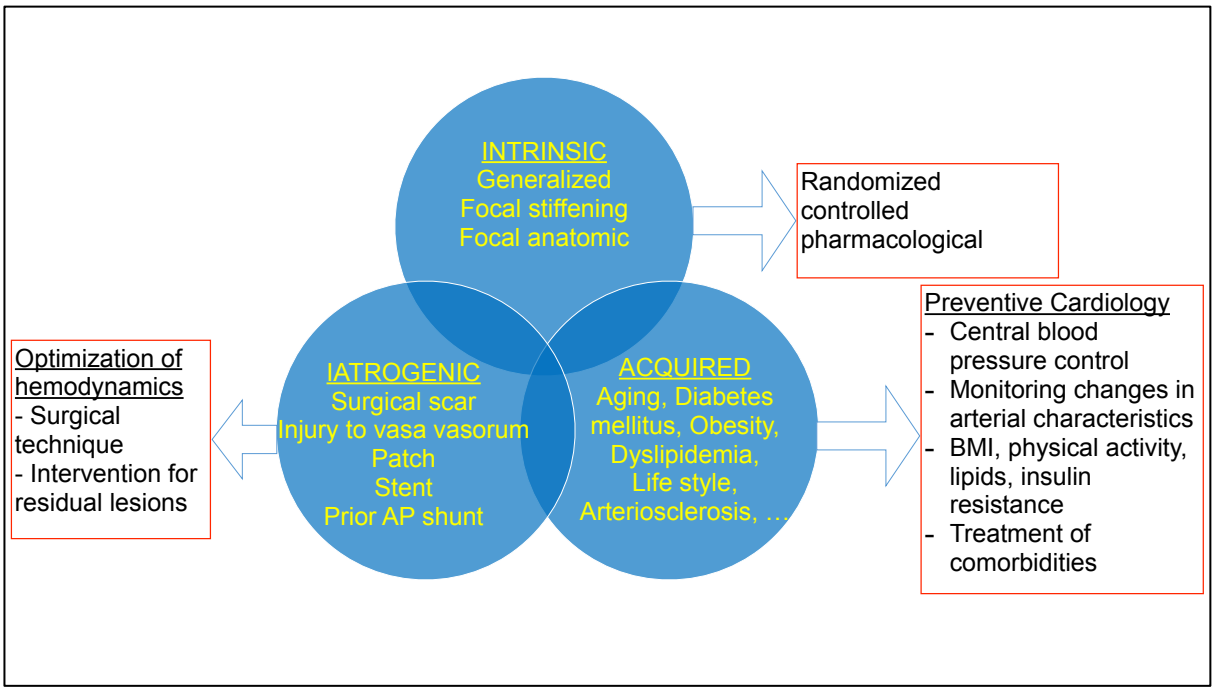

Figure 19: Illustration of different etiologies of arterial stiffness in CHD and suggested multifaceted management strategies. BMI: Body Mass Index.

Studying patients with congenital or early acquired CV risk factors from young age gives us the opportunity to detect potentially treatable disease mechanisms early. We advocate for an individualized approach, targeting each individual's iatrogenic and acquired risk factors to achieve the best possible long-term outcome for each patient (Figure 19).

Currently, we continue to develop our preventive congenital cardiology clinical research program that uses a systematic but individualized approach to optimize each patient. The aim is to withdraw from the "one size fits all" approach and move on to individualized medicine with the help of physiological and biochemical biomarkers. Targeted interventions may include exercise training programs as well as pharmacological strategies, while monitoring biomarkers longitudinally.

In addition, I plan to direct my research interest towards children with CHD and overweight or obesity. According to the model presented above, this is presumably a group at high risk for acquired CV morbidity during adulthood. Children in this high risk group should be enrolled into pediatric obesity programs early, either in outpatient or inpatient pediatric rehabilitation programs. It is my aim to follow parameters of arterial and ventricular function longitudinally in response to treatment, with the ultimate goal of reducing CV morbidity and mortality in overweight and obese patients with CHD.

The work presented herein has also set the foundation for further investigations that aim to better understand the pathophysiology of arterial changes and arterio-ventricular interaction in young patients with CHD or CV risk factors acquired early in life. We have an ongoing collaboration with the Pediatric heart Centre in Lund, Sweden, and Lund University, where I continue to hold a position as Associate Professor. Current projects relevant to the field include:

- Projects related to children with acquired CV risk factors
- Computational fluid dynamics of aortic arch flow following CoA repair
- Fetal magnetic resonance tomography in left sided obstructive CHD
- Invasive validation of central blood pressure measurements, AIx and PWV in children using different non-invasive devices. This project is crucial in order to determine whether algorithms established in adults actually apply to children as well.
- Arterial changes following pediatric heart transplantation
- Effect of high altitude – and thereby hypoxia – on arterial characteristics in children.
- Comparison of different electronic stethoscopes and use of artificial intelligence as a way to discriminate pathologic from physiologic murmurs.

6. Abbreviations

Abbreviation	Full name
AIx	Augmentation index
AIx75	Augmentation index corrected to a heart rate of 75/min
BAV	Bicuspid aortic valve
BMI	Body mass index
BNP	Brain Natriuretic Peptide
BP	Blood pressure
CAD	Coronary artery disease
CCS	Childhood cancer survivors
cfPWV	Cardio-femoral pulse wave velocity
CHD	Congenital heart disease
cIMR	Carotid intima-media roughness
cIMT	Carotid intima-media thickness
CKD	Chronic kidney disease
CoA	Coarctation of the aorta
CSP	Central systolic pressure
CV	Cardiovascular

CVD	Cardiovascular disease
EF	Ejection fraction
FMD	Flow mediated vasodilation
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LV	Left ventricle
MFS	Marfan syndrome
NO	Nitric oxide
oCHD	Other congenital heart disease
PAT®	Peripheral arterial tone
PWV	Pulse wave velocity
RHI	Reactive hyperemia index
SGLT2	Sodium-glucose co-transporter 2
SV	Single ventricle
TCPC	Total cavopulmonary connection
TGA	Transposition of the great arteries
TNNI3	Troponin I3 gene
TOF	Tetralogy of Fallot

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8. Publications

8.1 Original publications (first or senior authorship)

1. **Weismann CG**, Hlebowicz J, Åkesson A, Liuba P, Hanseus K. Comprehensive characterization of arterial and cardiac function in Marfan Syndrome - can biomarkers help improve outcome? Front Physiol. 2022 Apr 25;13:873373. PMID: 35547588. *Impact factor 4.134*
2. Lindow A, Kennbäck C, Åkesson A, Nilsson PM, **Weismann CG**. Common carotid artery characteristics in patients with repaired aortic coarctation compared to other cardiovascular risk factors. Int J Cardiology Congenital Heart Disease, Volume 7, March 2022, 100319. *Impact factor: new journal*
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11. Abraham S and **Weismann CG**. Left Ventricular End-Systolic Eccentricity Index for Assessment of Pulmonary Hypertension in Infants. Echocardiography 2016, Januar 16 (epub ahead of print). PMID: 26773570. *Impact factor 1.3*

12. Chamberland CR, Sugeng L, Abraham S, Li F, **Weismann CG**. Three-dimensional Evaluation of Aortic Annular Shape in Children with Bicuspid Aortic Valves With and Without Aortic Coarctation. Am J Card 2015; 116:1411-7. PMID: 26375172. *Impact factor 3.2*
13. **Weismann CG**, Lombardi KC, Grell BS, Northrup V, Sugeng L. Aortic stiffness and left ventricular diastolic function in children with well-functioning bicuspid aortic valves. Eur Heart J Cardiovasc Imaging 2016; 17:225-30. PMID: 26072912. *Impact factor 4.1*
14. **Weismann CG**, Bamdad MC, Abraham S, Ghiroli S, Dziura J, Hellenbrand WE. Normal Pediatric Data for Isovolumic Acceleration at the Lateral Tricuspid Valve Annulus – a Heart Rate Dependent Measure of Right Ventricular Contractility. Echocardiography 2014; 32(3):541-7. PMID: 25039533. *Impact factor 1.3*
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8.2 Co-authored publications

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2. Sjoberg, P, Hedstrom E, Fricke K, Frieberg P, **Weismann CG**, Liuba P, Carlsson M and Toger J. Comparison of 2D and 4D Flow MRI in Neonates Without General Anesthesia. J Magn Reson Imaging 2022 Jun 21;28303. PMID: 35726779. *Impact factor 5.119.*
3. Fricke K, Mellander M, Hanseus K, Tran PK, Synnergen M, Johansson Ramgren J, Rydberg A, Sunnegardh J, Dalen M, Sjoberg G, **Weismann CG**, Liuba P. Impact of Left Ventricular Morphology on Adverse Outcomes Following Stage 1 Palliation for Hypoplastic Left Heart Syndrome: 20 Years of National Data from Sweden. JAHA 2022 Apr 5;11(7):e022929. PMID: 35348003. *Impact factor 5.501*
4. Broberg O, **Weismann CG**, Øra I, Wiebe T, Liuba P. Characterization of Cardiac, Vascular and Metabolic Changes in Young Childhood Cancer Survivors. Front Pediatr 2021 Dec 8;9:764679. PMID: 34956978. *Impact factor 3.418*
5. Jeremiasen I, Naumburg E, Westoo C, **Weismann CG**, Tran-Lundmark K. Vasodilator therapy for pulmonary hypertension in children: a national study of patient characteristics and current treatment strategies. Pulm Circulation (accepted for publication Oct 19, 2021). *Impact factor 3.017*

6. Elkinany S, **Weismann CG**, Curtis A, Smith T, Zafar MA, Breen T, Li Y, Tranquilli M, Rizzo JA, Mukherjee SK, Ziganshin B, Elefteriades JA. Is Aortic Z-score an Appropriate Index of Beneficial Drug Effect in Clinical Trials in Aortic Aneurysm Disease? Am J Cardiol 2021 Jan 8;S0002-9149(20)31353-9. PMID: 33352210. *Impact factor 2.778*

7. Luceri MJ, Tala JA, **Weismann CG**, Silva CT, Faustino EV. Prevalence of Post-Thrombotic Syndrome After Cardiac Catheterization. Pediatr Blood Cancer 2015; 62:1222-7. PMID: 25663038. *Impact factor 2.4*

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8.3 Case reports

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8.4 Invited review articles

1. **Weismann CG** and Gelb BD. The genetics of congenital heart disease: a review of recent developments. Curr Opin Cardiol. 2007; 22(3):200-6. PMID: 17413276. *Impact factor 2.7*

8.5 Book chapters

1. **Weismann CG** and Gelb BD. Noonan Syndrome and related disorders: the Ras-MAPK pathway. Book chapter in Clinical Genomics: Practical Applications in Adult Patient Care (2013)

8.6 Letters to the Editor

1. **Weismann CG**, Hager A. Letter to the Editor in response to "Segmental Aortic Stiffness in Children and Young Adults With Connective Tissue Disorders: Relationships With Age, Aortic Size, Rate of Dilation, and Surgical Root Replacement" by Prakash et al., 2015. Circulation 2016; 133:e404. PMID: 26884629. *Impact factor 14.4*
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3. **Weismann CG**, Colson E, Shapiro ED. Letter to the Editor in response to "Publication performance of women compared to men in German cardiology" by Boehm et al., 2014. Int J Cardiol 2014; 182:227-8. PMID: 25617604. *Impact factor 4.0*

8.7 Collaborator on multi-center studies

8.7.1 Pediatric Heart Network

1. Handisides JC, Hollenbeck-Pringle D, Uzark K, Trachtenberg FL, Pemberton VL, Atz TW. Health-Related Quality of Life in Children and Young Adults with Marfan Syndrome. J Pediatr. 2019 January;204:250-255. PMID: 30270167. *Impact factor 3.890.*
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