Diploma thesis

Hemodynamic responses to orthostatic stress exposition in patients with severe aortic stenosis and coronary artery disease

Submitted by

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Berlin, 22.08.2022 *Jakob Geßner eh.*

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List of abbreviations

ACS	acute coronary syndrome
ADH	antidiuretic hormone
ANOVA	analysis of variance
ANP	atrial natriuretic peptide
ANS	autonomic nervous system
AS	aortic stenosis
AV	atrioventricular
AVA	aortic valve area
AVN	atrioventricular node
AVR	aortic valve replacement
BNP	brain-natriuretic peptide
BP	blood pressure
CABG	coronary artery bypass graft
CAD	coronary artery disease
CBF	coronary blood flow
CCS	chronic coronary syndrome
CI	cardiac index
CO	cardiac output
CVP	central venous pressure
DBP	diastolic blood pressure
ECG	electrocardiogram
EMG	electromyography
HCM	hypertrophic cardiomyopathy
HF	heart failure
HR	heart rate
HRV	heart rate variability
HUT	head-up-tilt
ICG	impedance cardiography
ICU	intensive care unit
IHD	ischemic heart disease
LV	left ventricle
LVEDV	left ventricular end-diastolic volume
LVESV	left ventricular end-systolic volume
LVH	left ventricular hypertrophy
MAP	mean arterial pressure
MBP	mean blood pressure
MI	myocardial infarction
MSNA	muscle sympathetic nerve activity
OH	orthostatic hypotension
OHT	orthostatic hypertension
OI	orthostatic intolerance
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
RAAS	renin-angiontensin-aldosterone-system

SAVR	surgical aortic valve replacement
SBP	systolic blood pressure
SI	stroke volume index
SN	sinus node
SV	stroke volume
SVR	systemic vascular resistance
TAVR	transcatheter aortic valve replacement
TPR	total peripheral resistance
TPRI	total peripheral resistance index
ZVA	valvuloarterial impedance

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Zusammenfassung

Hintergrund: Störungen der orthostatischen Blutdruckregulation entstehen aufgrund von Beeinträchtigungen der autonomen und kardiovaskulären Funktion, die in Patient*Innen mit Aortenstenose und Koronarer Herzerkrankung präsent sein können. Orthostatische Hypotonie wurde als ein Risikofaktor für eine zukünftige Koronare Herzerkrankung identifiziert. Hämodynamische Studien der orthostatischen Blutdruckregulation in Patienten mit manifester Koronarer Herzerkrankung oder Aortenstenose existieren kaum.

Zielsetzung: Diese Diplomarbeit hat die Untersuchung der hämodynamischen Reaktion auf orthostatischen Stress bei Proband*Innen mit hochgradiger valvulärer Aortenstenose oder koronarer Herzerkrankung zum Ziel. Als Arbeitshypothese wird angenommen, dass die Präsenz dieser kardiovaskulären Krankheitsentitäten die orthostatische hämodynamische Kontrolle stört, und dass sich die pathogenetischen Unterschiede in den Krankheitsentitäten in sichtbaren Unterschieden in der hämodynamischen Reaktion auf das Protokoll äußern.

Methodik: Insgesamt 12 Probanden mit koronarer Herzkrankheit (0 Frauen) und 11 Proband*Innen mit hochgradiger Aortenstenose (5 Frauen), die Teil der CardioVib-Studie waren, wurden einem Aufstehversuch aus dem Liegen unter extensivem hämodynamischem Monitoring mittels des Task Force® Monitors unterzogen. Systolischer, diastolischer, und mittlerer Blutdruck, Herzrate, Schlagvolumen/-index, Herzzeitvolumen/-index und totaler peripherer Widerstand/-index wurden über acht 10-sekündige Epochen erhoben und nachfolgend analysiert. Eine ANOVA mit Messwiederholungen wurde durchgeführt, um die hämodynamischen Änderungen innerhalb der jeweiligen Gruppe zu untersuchen. Eine 2-faktorielle ANOVA mit Messwiederholungen wurde durchgeführt, um unterschiedliche hämodynamische Reaktionen auf das Protokoll zwischen den Gruppen zu ermitteln. Proband*Innen mit hypertensiver Reaktion auf das Stehen wurden isoliert in Abhängigkeit ihrer zugehörigen Krankheitsentität mit einer 2x2 ANOVA mit Messwiederholungen für Herzzeitvolumenindex und totalen peripheren Widerstandsindex analysiert.

Ergebnisse: Proband*Innen mit Aortenstenose zeigten im Mittel eine hypertensive Reaktion auf das Stehen, wobei 64% der Proband*Innen die Definition für orthostatische Hypertonie erfüllten. Die Probanden mit koronarer Herzerkrankung zeigten im Mittel keine Störung der orthostatischen hämodynamischen Homöostase. Allerdings erfüllten 33% der Probanden die Definition für orthostatische Hypertonie, während 17% die Definition für orthostatische Hypotonie erfüllten.

Es existierten signifikante Unterschiede in Herzzeitvolumen und totalem peripherem Widerstand/-index zwischen den Gruppen, die sich allerdings nicht in einer signifikant unterschiedlichen Reaktion auf das Protokoll äußerten. Die hypertensive Reaktion scheint, ausgehend von den Messergebnissen, primär durch eine Erhöhung des vaskulären Widerstandes bei gleichzeitiger Stabilität des Herzzeitvolumens vermittelt. Auf individueller Ebene zeigten sich aber stark heterogene Mechanismen.

Schlussfolgerung: Die Ergebnisse zeigen, dass Störungen der orthostatischen Blutdruckregulation bei Patient*Innen mit den oben beschriebenen kardiovaskulären Erkrankungen anzutreffen sind. Die hämodynamische Reaktion auf orthostatischen Stress unterschied sich, am ehesten aufgrund der hohen Prävalenz von Störungen orthostatischen Blutdruckregulation in beiden Gruppen, nicht signifikant zwischen den Gruppen. Aufgrund des Designs der Studie und der multiplen Limitationen, sollten die Ergebnisse durch zukünftige Studien bestätigt und pathophysiologisch exploriert werden.

Abstract

Background: Orthostatic blood pressure dysregulations emerge from autonomic and cardiovascular impairments, which may be present in patients with severe aortic stenosis and coronary artery disease. Orthostatic hypotension has been identified as a predictor of future coronary disease, but hemodynamic studies of postural control in patients with manifest aortic stenosis or coronary artery disease are lacking.

Aims and Objectives: This diploma thesis aims to explore the hemodynamic reaction to orthostatic stress in patients with severe aortic stenosis or coronary artery disease as part of the CardioVib trial. We hypothesize that the presence of these cardiovascular conditions impairs orthostatic hemodynamic control, and that differences in the underlying pathologies relay to observable differences in the reaction to orthostatic stress.

Methods: A total of 12 patients with coronary artery disease (0 female) and 11 patients with severe aortic stenosis (5 female), enrolled in CardioVib, were subjected to a supine-to-stand test under extensive hemodynamic monitoring using the Task Force® Monitor. Systolic, diastolic, mean blood pressure, heart rate, stroke volume, stroke index, cardiac output, cardiac index, total peripheral resistance and total peripheral resistance index were analysed over the course of the protocol using an epochal structure of eight 10-second intervals. Repeated measures ANOVAs were conducted to assess within group changes over the course of the protocol and a mixed-design ANOVA was performed to assess group differences in the reaction to stand. Hypertensive responders to standing were identified and cardiac index total peripheral resistance index were analysed using a 2x2 mixed-design ANOVA.

Results: On average, subjects with aortic stenosis displayed a hypertensive response to standing, with 64% showing overt orthostatic hypertension. In the CAD group no disturbance of the aggregate orthostatic hemodynamic response was observed, but 33% displayed overt orthostatic hypertension, while 17% were deemed hypotensive responders. Significant group differences for cardiac output, total peripheral resistance and total peripheral resistance index existed, yet the reaction to orthostatic stress over the course of the protocol did not differ significantly between groups. The hypertensive response was individually heterogeneously mediated but on average primarily powered by the increase of vascular resistance in the presence of relatively stable cardiac index upon standing.

Conclusions: Our findings indicate that orthostatic blood pressure dysregulations may be frequently observed in patients with aforementioned cardiovascular conditions.

The reaction to orthostatic stress did not differ between groups, likely due to the high presence of similar orthostatic blood pressure dysregulations in both cohorts. Due to the observational design and several limitations of this analysis, these relationships require more research and ought to be confirmed as well as pathophysiologically explored in future studies.

1. Introduction

The cardiovascular system serves as the foundation for the functioning of the human body. It supplies the tissues' demand for oxygen and nutrients like glucose, fatty acids and amino acids, whilst disposing of waste products and carbon dioxide to maintain an optimal environment for the cellular functions.(1) The body's hormonal regulatory systems also rely on the distribution of signalling substances and enzymes through the bloodstream to allow for adjustments of tissue function and activity.(2, 3) Changes in the body's posture, individual organ's acitivity or stress from exercise demand regular adjustments of all components of the cardiovascular system. For this purpose multiple intertwined regulatory systems such as the autonomic nervous system, the hypothalamic-pituitary-adrenal axis and the renal system allow for temporary or long-lasting adjustments to the cardiovascular systems' function.

1.1 Anatomy

1.1.1. Cardiac and coronary anatomy

The heart lies at the centre of the cardiovascular system and acts as the driving force of blood circulation in the vascular system. It is a muscular hollow organ situated in the ventral thoracic cavity with two ventricles that simultaneously pump blood into the two separated blood circuits and two atria atop the ventricles that drain blood into the chambers.(3) The atria collect either deoxygenated or oxygenated blood from the hollow or pulmonary veins respectively and release it via the atrioventricular valves into the ventricles during diastole.(3) The ventricles hold most of the hearts muscle mass and propel the blood through the pulmonary and systemic circulation. The aortic and pulmonary semilunar valves are situated between the ventricles and the ascending aorta and pulmonary trunk respectively and prevent backflow from the great arteries into the ventricles. All valves open and close entirely passively following changes of the pressure gradients between the chambers, which they separate.(1) Above the aortic valve and aortic sinuses lay the coronary ostia of the left and right main coronary arteries, which supply the heart with blood to meet its varying nutrient demands. The left main coronary artery typically branches into the left anterior descending artery, which trails down the anterior wall and supplies the septum and anterior wall of the left ventricle, and the left circumflex artery, which follows the furrow between left atrium and ventricle and perfuses the left free wall.(3)

The right main coronary artery descends between the right atrium and the ventricle, gives off branches to supply the right ventricle and atrium and typically gives off the posterior descending artery to perfuse the inferior and posterior wall of the left ventricle. There are however many interindividual differences in coronary artery anatomy and therefore a large variability in which area is supplied by which artery is seen.(3) These epicardial coronary arteries branch into the intramyocardial arteries that serve as primary resistance vessels and control the coronary blood flow. After leaving the capillary bed, the coronary vasculature converges into the cardiac veins, that drain the deoxygenated venous blood either directly or via the coronary sinus into the right atrium.(1, 2)

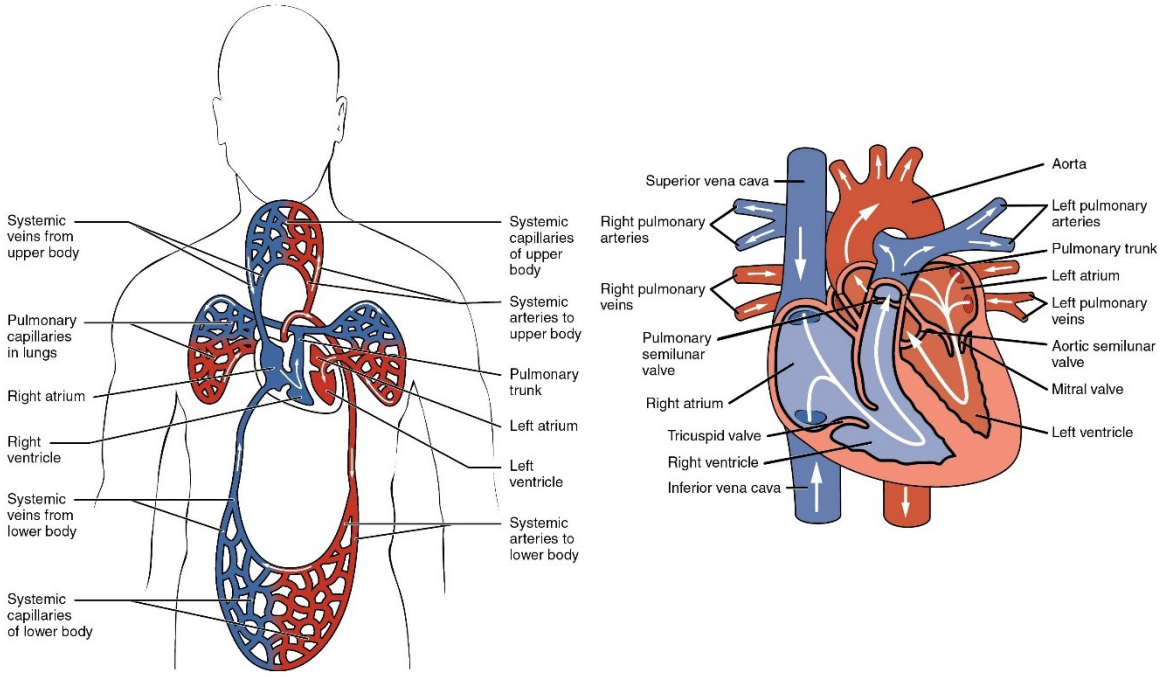


Figure 1: Fundamental cardiac and vascular anatomy, obtained under CC BY from https://commons.wikimedia.org/wiki/File:2003_Dual_System_of_Human_Circulation.jpg, edited by the author

1.1.2. Anatomy of the vascular system

The vascular system comprises a high-pressure circuit, composed of the left ventricle during systole, the aorta, arteries and arterioles, and a low-pressure circuit, which entails the capillaries, veins, right side of the heart and the entire pulmonary circulation.(4) Different perfusion pressures and flow velocities in these circuits require distinguishable vessel-types that are suited to accommodate these differing circumstances. Arteries lead blood away from the heart and are fitted with thicker walls, layered with smooth muscle tissue, to withstand and regulate the high pressures necessary to allow for the systemic distribution of the blood.(1,

4) Accordingly, they are mostly found in the high-pressure branch of the circulatory system.(4) The ascending aorta is even equipped with elastic tissue to catch on the pulsatile flow, produced by the beating heart, and transform it into a continuous flow during the diastole.(5) Veins are the thin-walled capacitance vessels that, under low pressure, return the blood to the heart.(1) Together with the smaller venules and capillaries they serve as a blood reservoir, holding up to 85% of the overall blood volume.(4) The different vessel types are arranged in two blood circuits; the systemic or greater circulation, which supplies all tissues except the lungs, and the pulmonary circulation, which supplies the latter (see Figure 1).(1) The systemic circulation originates from the left ventricle, pumping oxygenated blood into the ascending aorta and its' branching arteries and smaller arterioles to distribute the blood to peripheral tissues. The capillaries merge into the postcapillary venules from which blood is progressively shifted to the larger veins and returned to the right atrium.(1) The pulmonary circuit, originating from the right ventricle, then perfuses the pulmonary arteries and the capillary system of the lungs with deoxygenated blood to allow for the exchange of respiratory gases. The pulmonary veins drain the oxygenated blood into the left atrium to supply the systemic circulation.(4)

1.2 Cardiovascular physiology

1.2.1. Cardiac conduction and cardiac cycle

The heart's contraction cycle, deemed the cardiac cycle, is divided in two general phases: systole, the phase of muscular contraction and diastole, the phase of myocardial relaxation.(3) Systole can be further divided into the phase of isovolumic contraction and the following ejection phase. Diastole can be split into four distinct phases, namely the phase of isovolumic relaxation, rapid inflow, the diastasis and atrial contraction.(6) The cardiac cycle is controlled by specialised autorhythmic muscle cells in the heart's intrinsic conductive system and is initialized by the sinus node (SN), located atop the right atrium near the orifice of the upper hollow vein.(1, 3) The generated action potentials (AP) travel rapidly through the atria to the atrioventricular node (AVN) (P-wave), which serves as the only pathway for the conductive system to the ventricles.(2, 3) The AVN delays the conduction to the ventricles by about 0.1s, and the thereby the excitation of the ventricles' musculature (QRS-complex).(1) After depolarization, contraction ensues and is followed by the repolarization (T-wave) and subsequent relaxation of the muscle cells.

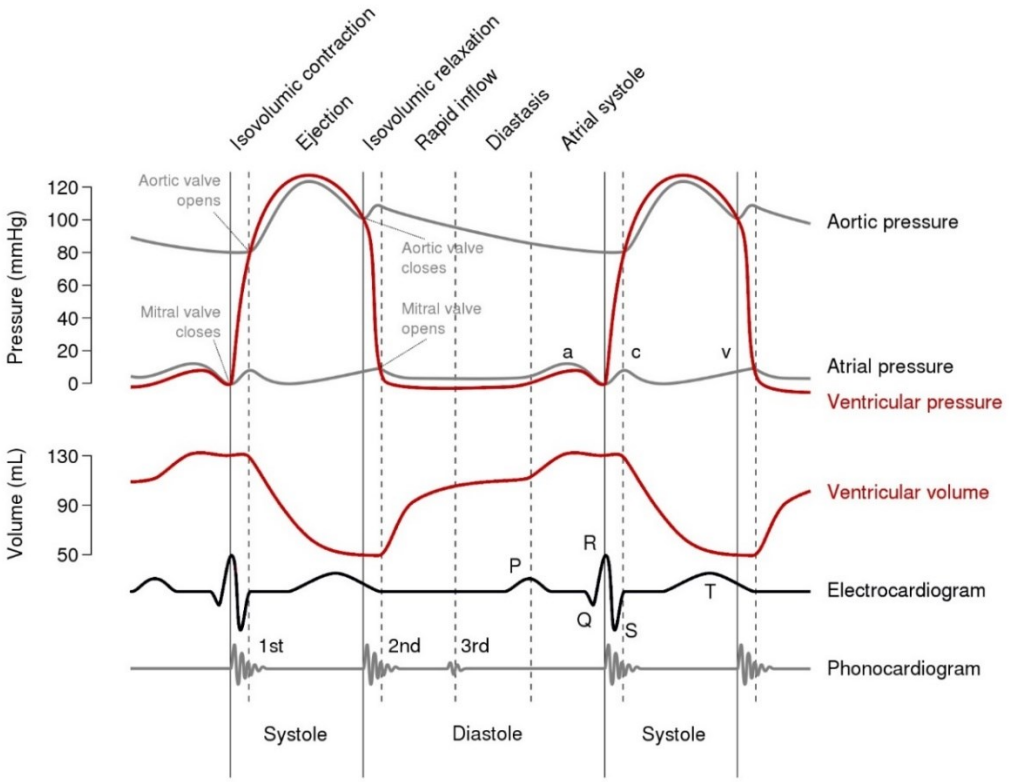


Figure 2: Cardiac cycle, pressure and volume changes over two heart beats and electrocardiographic changes and heart sounds (phonocardiogram) emerging from cardiac contraction. Obtained under CC BY-SA from https://commons.wikimedia.org/wiki/File:Wiggers_Diagram.svg, edited by the author.

The atria fill during ventricular systole, as the AV valves remain closed due to high pressures in the ventricles. During early ventricular diastole or **isovolumic relaxation**, all valves are closed, the ventricles relax, and the ventricular pressure subsides rapidly. Once the ventricular pressure falls below the atrium's pressure, the AV valves are pushed open by the AV pressure gradient, which initiates the diastolic ventricular filling phase and results in **rapid inflow** to the ventricles.(1) The ventricular filling is supported by the passive motion of the AV plane towards the cardiac base during relaxation.(5, 7) As the ventricular and atrial pressures equalize, inflow subsides. The phase of equilibrium between ventricles and atria is termed **diastasis**.(6) The end of the diastole is marked by the **atrial systole**, which accounts for 10-20% of the ventricular filling.(1, 2, 4) After the atrial contraction, the atrial pressure falls, reversing the pressure gradient across the AV-valves and causing them to float towards the cardiac basis. The beginning of the **isovolumic contraction** immediately increases intraventricular pressure, closing the AV valves completely, once the ventricular pressure exceeds atrial pressure.(1, 2)

During this phase the ventricular pressure is relatively low and does not reach the semilunar valve's opening threshold. Therefore, the semilunar valves remain closed, no blood is ejected, the ventricular volume remains unchanged, and intraventricular pressure builds up as the myocardium contracts.(1) Once the ventricular pressures surpass those in the ascending aorta and pulmonary trunk respectively, the semilunar valves are pushed open and the **ejection phase** begins, during which the stroke volume is ejected, and the maximal aortic pressure is reached.(1, 2) During the ejection phase the atria are being expanded as the AV plane is pulled towards the ventricular apex, passively filling them with blood. The end of ejection marks the end of the systole, which is succeeded by the onset of the diastole.(2) As the ventricles begin to relax, ventricular pressures subside rapidly, causing blood to push back from the large arteries and thereby forcing the semilunar valves shut, causing a notch, which is deemed 'incisura' in the arterial pressure curve.(3) After the closure of the valves, the ventricles continue to relax without changes in the ventricular volumes. This phase of **isovolumic relaxation** continues until the ventricular pressures fall below the atrial pressures and the cardiac cycle begins anew.(1, 2)

1.2.2. Cardiac output

In healthy individuals the end diastolic volume (EDV) of each ventricle increases to about 110-120 ml. The stroke volume (SV) can be calculated by subtracting the end-systolic volume (ESV) from the EDV. The SV of healthy adults amounts to ~70-80 ml, pumped into the aorta and pulmonary artery.(1, 2)

$$SV = EDV - ESV$$

The ejection fraction (EF) refers to the fraction of the EDV, that is expelled from the ventricle during systole and normally amounts to 60-70%.(1, 7) The cardiac output (CO) is the amount of blood ejected each minute and ranges from 4,5-6 l/min at rest.(7) It is calculated by multiplying SV by the number of hearts beats per minute (HR):

$$CO = SV \times HR$$

Cardiac output is highly dependent on body surface area (BSA) and can therefore be divided by BSA to achieve normalization for body composition. The resulting cardiac index (CI) normally ranges from 2,6 to 4,2 L/min/m².(2, 7) CO must be highly adaptable in order to meet the varying demands of the human body for oxygen during physical exertion or stress. The adaptation of HR and SV constitute the regulation of CO.

This is achieved intrinsically by the Frank-Starling mechanism and extrinsically by the autonomic nervous system (ANS). (1, 2, 5, 7) Since the reserve capacity for heart rate changes outweighs the reserve for changes in the stroke volume, alterations to HR are the primary means of increasing CO.

1.2.3. Total peripheral resistance

Blood flow (F or Q), the amount of blood transferred per time unit, is dependent on the pressure difference (ΔP) between the arterial (mean arterial pressure=MBP) and the venous system (central venous pressure=CVP), and the conductance of the vessels. The latter quantifies the ease of flow. Its inverse is the resistance (R), the difficulty experienced by the blood in overcoming said resistance.(3) This relationship is described by the following modification of Ohm's law:

$$\boldsymbol{R = \frac{\Delta P}{F}}$$

Therefore total peripheral resistance can be defined as the pressure difference required to drive a unit of flow, and is quantified in either $mmHg*ml*min^{-1}$ or $dyn*s*cm^{-5}$.(2, 3) Higher resistance necessitates a higher pressure difference to drive any given flow.(3) Resistance is dependent on the width of the combined cross section of the blood vessels, its length, circuitry arrangement and the blood's viscosity.(2) The contribution of the large arteries to resistance is quasi negligible (~2%). Arterioles, due to their immense combined cross-section, exert the most influence on the systemic resistance (~60%) by altering their diameter.(3) They are therefore regarded to as primary resistance vessels.(2) Primary resistance vessels are continuously in state of slight smooth muscle contraction, called vascular tone, to maintain the vascular resistance. This tone is modified by extrinsic mechanisms such as the ANS activity and hormones, but also by intrinsic local mechanisms put in place to adapt local tissue perfusion.(2)

1.2.4. Arterial blood pressure

The circulating blood volume continuously exerts force on the walls of the blood vessels it moves through. In the arterial branch, this pressure is referred to as the arterial blood pressure and is commonly measured in mmHg. The heart's pulsatile ejection of blood into the ascending aorta entails a peak in blood pressure, named systolic blood pressure (SBP). The blood pressure falls to its lowest during the heart's diastole, hence the lowest blood pressure is called diastolic blood pressure (DBP).(1, 2) Since systole is shorter than diastole, the mean

blood pressure over one cardiac cycle (MBP) cannot be averaged from SBP and DBP, but must be estimated under appreciation of the length of each phase of cardiac contraction. MBP can also be calculated from a hydrodynamic modification to Ohm's law above, by substituting F with CO, ΔP with MBP-CVP and R with TPR, which is then expressed as:

$$MBP = (CO \times TPR) + CVP$$

MBP is consequently mainly determined by cardiac output (CO) and total peripheral resistance (TPR).(2) Given constant CO, vasodilatation by relaxation of the arteries' or arterioles smooth muscle lining, entails a reduction of TPR and thereby MBP, while vasoconstriction inversely increases TPR and consequently MAP.(2) In reality MBP is sought to be relatively stable, which necessitates constant adaptation of CO and TPR through intrinsic and extrinsic regulatory mechanisms.(3)

1.2.5. Regulatory mechanisms of the cardiovascular system

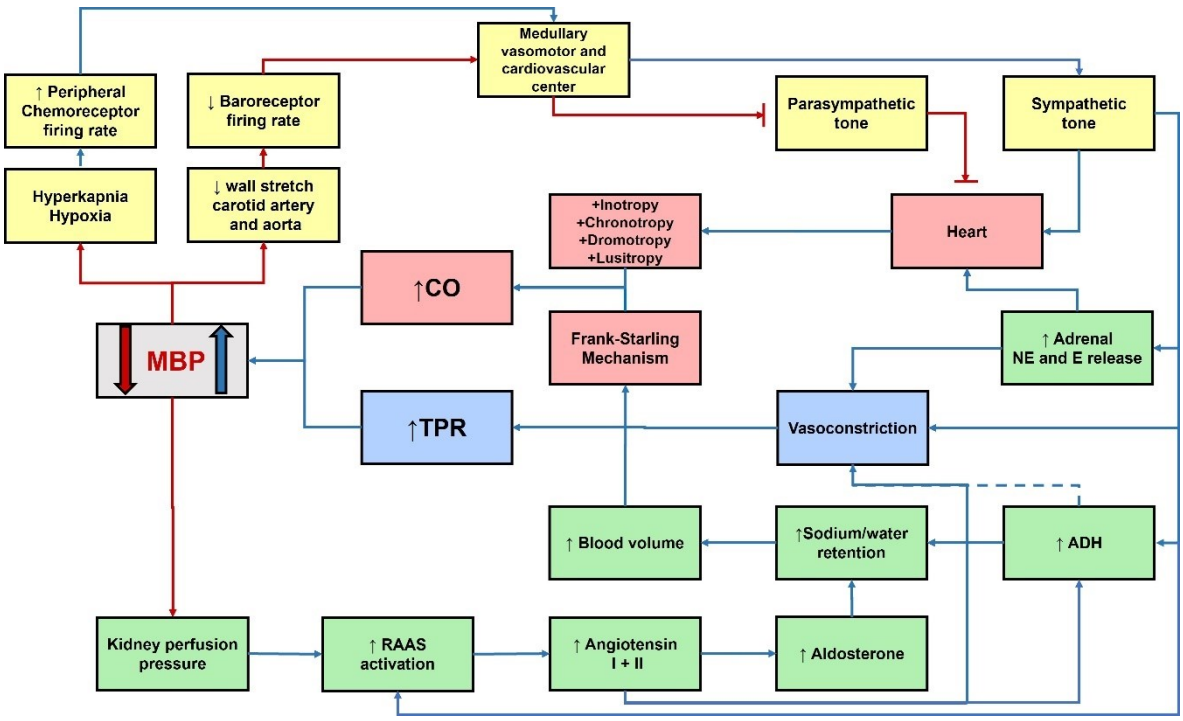


Figure 3: Overview of the physiological adaptations to hypotension, red arrows indicate down-regulation, blue arrows indicate up-regulation, dotted line represents a weak effect, yellow background represents pathways of the central and peripheral nervous system, green background represents humoral pathways, red and blue backgrounds indicate cardiac and vascular countermeasures respectively. ADH=antidiuretic hormone, CO=cardiac output, E=epinephrine, MAP=mean arterial pressure, NE=norepinephrine, RAAS= renin-angiotensin-aldosterone-system, TPR=total peripheral resistance. Illustration by the author.

1.2.5.1. Cardiac autoregulation - Frank Starling Mechanism

Spontaneous alterations of CO are possible due to the heart's inherent capacity to alter its SV from beat to beat depending on preload and afterload. Preload refers to the end-diastolic stretching of the cardiac myocytes, while afterload is referred to as the resistance which the ventricles must overcome to eject their stroke volume.(2, 5, 6) The capability of the heart to adapt the SV depending on changes in preload and afterload is called Frank-Starling mechanism. It is independent from the ANS and aims to keep the stroke volume of both ventricles equal.(1, 5) Greater stretching of the myocardium increases sarcomere length, which has been shown to sensitize troponin C to intracellular calcium. The increased affinity leads troponin to bind more calcium, and the actin-myosin-complex to develop more contractile force.(2, 4, 5, 7) This results in an increase of SV if preload and thus end-diastolic pressure increase, and a reduction of SV if venous return diminishes.(6) This prevents a shift of blood volume between the circulatory circuits. As right ventricular output increases, so does the venous return to left ventricle, thereby increasing left ventricular preload, SV, and thus matching the outputs of both ventricles. (2) Increased afterload, for instance due to heightened aortic pressure, entails a momentary reduction in SV.(1, 2) Constant venous return then generates a diastolic volume overload by adding ventricular filling to the greater ESV. This in turn generates more contractile force, due to an elevated preload, that normalizes SV in the presence of elevated aortic pressures.(5, 7) Conversely, a reduction in afterload entails a momentary increase in SV.(2) In the healthy individual, preload and afterload change in unison and not isolated.(6)

1.2.5.2 Autonomic nervous system regulation of cardiac and vascular function

The extrinsic regulation of cardiac function and vascular tone is strongly dependent on the ANS and its components: the sympathetic and parasympathetic nervous system. The ANS exerts direct control over the TPR and CO by innervating both the heart and the blood vessels. Sympathetic stimulation displays a relatively high latency, while parasympathetic alterations, like stimulation or its withdrawal, translate rapidly.(3)

1.2.5.2.1. Sympathetic nervous system

The sympathetic cardiac nerve originates from the cervical and thoracic sympathetic trunk. Postganglionic fibres directly innervate the SN, the AVN, as well as the ventricular myocardium.(2) Direct innervation of the heart increases HR (positive chronotropic), the AV transmission speed (positive dromotropic), the muscular contractility (positive inotropic), and the

muscular relaxation speed (positive lusitropic)(Figure 3).(3, 4) Depression of the sympathetic nervous system can lower HR and ventricular contractility and thereby lower CO by up to 30 percent.(1) In the vascular system sympathetic innervation primarily affects arterioles and small arteries, predominantly in the skin, the kidneys, and the splanchnic region.(1, 5) Sympathetic stimulation releases norepinephrine (NE) from postganglionic sympathetic nervous fibres, while preganglionic fibres trigger the release of catecholamines from the adrenal medulla. In blood vessels NE causes α_1-adrenergic receptors, present in most blood vessels, to induce vasoconstriction and consequently increases TPR.(5) Continuous sympathetic stimulation upholds the vascular tone, a state of continuous partial contraction of the blood vessel walls. Veins are also innervated by sympathetic fibres, causing them to contract upon stimulation, which aids in increasing venous return.(1)

1.2.5.2.2. Parasympathetic nervous system

The parasympathetic innervation of the heart stems from cervical and thoracic branches of the vagal nerve and is mostly limited to the SN, the AVN, the myocardium of the atria, and coronary vessels. (2) Owing to the cardiac distribution of its nervous fibres, the effects of vagal stimulation are mostly limited to altering the HR, while only exerting weak influence over ventricular contractility.(1, 7) Its stimulation slows down the HR (negative chronotropic), the AV transmission speed (negative dromotropic), and moderately lowers the force of muscular contraction (negative inotropic).(4) Parasympathetic influence on vascular function is quasi negligible, as cholinergic fibres only innervate blood vessel in few organs like the brain and genitals.(5)

1.2.5.2.3. Baroreceptor and chemoreceptor reflex

Nerve endings in the aortic arch and carotid sinuses constitute arterial pressure receptors. When MBP increases, the arterial wall is stretched, which activates the receptors and increases their afferent rate of nerve firing to the cardiovascular centre in the medulla, conducted by the 9^{th} and 10^{th} cranial nerve.(1) Stimulation entails an inhibition of sympathetic, and an increase of parasympathetic tone, which results in reduced CO, TPR and therefore MBP.(5) Conversely a reduction in MBP reduces the firing rate of the baroreceptors and reduces inhibition of sympathetic tone (Figure 3). Due to their sensitivity to short-term pressure changes, they play a key role in orthostasis, when blood is displaced during standing.(1, 5) The activity of the receptors is not bound to specific MBP values, but primarily responds to rapid pressure changes. Therefore they can ‘reset’ when blood pressures remain elevated

for longer periods of time, meaning they do not detect permanent blood pressure elevation but normalize their firing rate in the presence of hypertension.(5) Similar to baroreceptors, chemoreceptors are present in the aortic and carotid body. They react to hypoxia, hypercapnia and acidosis, and stimulate sympathetic fibres emerging from the vasomotor centre. This entails a temporary increase in HR, CO and MAP and release of epinephrine from the adrenal medulla.(7)

1.2.5.3 Humoral regulation of blood pressure and volume

Endocrine mechanisms are strong drivers of primarily long-term blood pressure adaption, mostly through adaptation of the body fluid and blood volume status.(1)

1.2.5.3.1. Circulating catecholamines

Short term alterations are also made possible by the release of circulating catecholamines, namely epinephrine and NE from the adrenal medulla, when preganglionic sympathetic nerves are activated (Figure 3).(2) The effects of the catecholamines depend on the receptors expressed on the surface of the blood vessels and the heart. Epinephrine release outweighs NE release and usually produces vasoconstriction through α-adrenoreceptors and positive inotropy through β_1-receptors.(5)

1.2.5.3.2. Renin-Angiotensin-Aldosterone System

Sympathetic stimulation, hypotension, the presence of catecholamines all trigger the secretion of renin from the kidneys' juxtaglomerular apparatus into the blood stream.(2) Renin cleaves off angiotensin I from angiotensinogen, which in turn is converted into the active vasoconstrictor angiotensin II by the angiotensin-converting enzyme, primarily located in the capillaries of the lungs.(2, 5) Angiotensin II serves as a potent constrictor of resistance vessels throughout the body.(5) It also exerts influence over other hormonal and organ systems, and thereby facilitates the release of vasopressin and furthers the release of aldosterone from the adrenal cortex.(2) Aldosterone raises sodium and secondarily water reabsorption in the tubules to elevate blood volume and by extension blood pressure.(1)

1.2.5.3.3. Vasopressin and natriuretic peptides

Vasopressin, or antidiuretic hormone (ADH), is a peptide hormone. It's secretion from the posterior lobe of the pituitary gland is triggered by sympathetic stimulation, angiotensin II secretion, high body fluid tonicity or decreased atrial filling. It binds to V_2-receptors in the kidney, increases water reabsorption in the collecting duct and thereby increases blood

volume and blood pressure. In high concentrations it can also bind to V_1-receptors and trigger vasoconstriction.(2) Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) counteract angiotensin II by increasing sodium excretion in the kidney, inhibiting AT II release and increasing GFR.(2) They are produced and released by atrial myoendocrine cells in response to stretching of the atrial wall, resulting from increased venous return or central volume overload.(4)

1.2.5.4. Local regulation of tissue perfusion

Local metabolic activity releases vasodilating metabolites and changes the chemical composition of the interstitial fluid. These mechanisms induce a localized vasodilation and therefore increase in blood flow.(5) The endothelium also produces nitric oxide as a response to heightened shear stress, which induces vasodilatation.(5)

1.2.5.4.1. Coronary blood flow regulation

The coronary circulation ensures that the heart's varying oxygen and nutrient demands are adaptively met.(1) The myocardial oxygen demand is determined by the ventricular wall stress, HR and the inotropic state, while myocardial oxygen supply is determined by the blood oxygen content and coronary blood flow (CBF). The hear cardiac muscle extracts up to 70% of the oxygen content from the blood at rest already, leaving little extraction reserve.(3) The increase of CBF is therefore the primary means by which greater myocardial oxygen demands are met.(1) Additionally 80-85% of CBF are conducted during diastole, due to the mechanical pressure exerted on the myocardial microvasculature and their subsequent compression during systole.(3) This effect on coronary flow is greatest in the LV, and appears to a lesser extent in the RV and the atria.(2) Analogous to the rest of the arterial system, CBF hinges on the combined cross section and thereby resistance of the coronary arterioles.(8) CBF regulation is achieved by a complicated and not yet completely understood autoregulatory alteration of coronary tone through the interplay of ANS influence and local metabolic control.(2) Parasympathetic and sympathetic innervation are present in the coronary arteries, though the effect of sympathetic vasoconstrictive influence outweighs that of parasympathetic vasodilation.(1, 2) Sympathetic activity induces a transient epicardial vasoconstriction, positive inotropic and chronotropic effects, which result in increased oxygen demand and the accumulation of metabolic vasodilators. These compounds result in a net vasodilation, which overrides the sympathetic epicardial constriction, and then readjusts the CBF to the myocardium's needs, called 'metabolic hyperemia'.(1-3, 8)

1.3. Orthostasis, orthostatic intolerance and orthostatic hypertension

Orthostasis refers to the adoption of an upright posture, the gravitational challenge imposed on the human body by standing in an upright position, and the physiological countermeasures to maintain postural and hemodynamic homeostasis.(3) The foremost vertical posture in humans brings with it the need for compensatory mechanisms to maintain orthostatic tolerance in the face of rapid blood volume transpositions, caused by standing.(9) As was laid out in Chapter 1.2.4, short-term adjustments to the circulatory system are primarily dependant on the ANS to maintain cardiovascular homeostasis.(10) Impairment of the physiological compensation, caused for instance by deconditioning, ageing, autonomic failure and diseases of the central and peripheral nervous system, can result in reduced tolerance and adverse symptoms when standing upright. This is denoted orthostatic intolerance (OI).(9)

1.3.1. Cardiovascular challenges of standing upright and physiological countermeasures

The physiological adaptive reaction to active standing can be categorized into different phases of hemodynamic and autonomic adjustments, beginning with the initial response within 0-30 seconds of standing, and the following phase of early stabilization from 30-180 seconds of standing.(11) After assumption of the standing position from a supine or sitting position, gravity induces a progressive translocation of thoracic blood volume to the lower extremities and abdomen, resulting in a shift of 500-1000 ml of blood to the capacitance vessels in the lower extremities, and the venous arm of the splanchnic circulation.(12) Consequently, the venous return to the heart and preload diminish. In accordance with the Frank-Starling mechanism, a reduction of SV would ensue.(13) During the transition and initial standing period, the muscle-pump activation in the lower limbs may initially stabilize venous return, temporarily augmenting SV to normal levels and, together with HR augmentation, increase CO by about 20%. This is usually overshadowed by the drop in TPR, hypothesized to be caused by rapid vasodilation after leg muscle contraction, cardiopulmonary baroreceptor response or arterial baroreceptor response, due to a short MBP burst during positional change.(11) The resulting drop in central blood pressure decreases the wall-tension in the aorta and carotid arteries and slows the firing rate of the baroreceptors to the vasomotor centre.(5, 12) The reduction in central blood volume is also detected by cardiopulmonary baroreceptors, that are primarily susceptible to volume changes, but only seem to play a minor role in maintenance of orthostatic homeostasis.(14) The dampening of baroreceptor

activity incurs a reduction in inhibitory signals to the medullary circulatory centre and results in a boost in peripheral and cardiac sympathetic activity and weakening of cardiac vagal nerve stimulation.(15) With the reactivation of the baroreflex, the early phase of stabilization is initialized. The result is an increase in TPR by about 40%, in HR by about 20%, an increase cardiac contractility, all of which maintain arterial pressure or may even elevate MBP by 10-14 mmHg. These adaptations ensure sufficient cerebral perfusion pressure.(3, 5, 13, 16) The increase in HR seems to be the results of parasympathetic withdrawal and increase of sympathetic tone, while the secondary increase in TPR in mediated by increased sympathetic stimulation.(17) CO may decline by up to 20% during prolonged standing.(16) This may be exacerbated by blood pooling in the lower limbs, which raises venous pressure in the feet up to 80 mmHg and thereby facilitates the shift of plasma into the interstitial space.(2) This contributes to diminishing venous return by a reduction of the circulating blood volume of about 10% after 30 minutes.(12, 14) This blood pooling in the lower extremities is limited by lower body skeletal muscle activation. The muscles contract rhythmically and compresses capacitance vessels to stabilize venous return, even during relative inactivity.(13) In otherwise healthy subjects, poor orthostatic tolerance was countered by greater activation of the lower limb muscles by more pronounced anteroposterior sway.(18) The skeletal muscle pump activation may somewhat ameliorate the reduction in SV seen in head-up-tilt (HUT) and results in less severe SV reduction during active standing.(7) Nonetheless, the increase in HR does not offset the SV reduction completely, especially in elderly individuals with attenuated HR responsiveness, and thus CO remains lower during standing than in the supine position.(4, 16) The reduction in standing CO during active standing periods after the initial response appears comparable or only

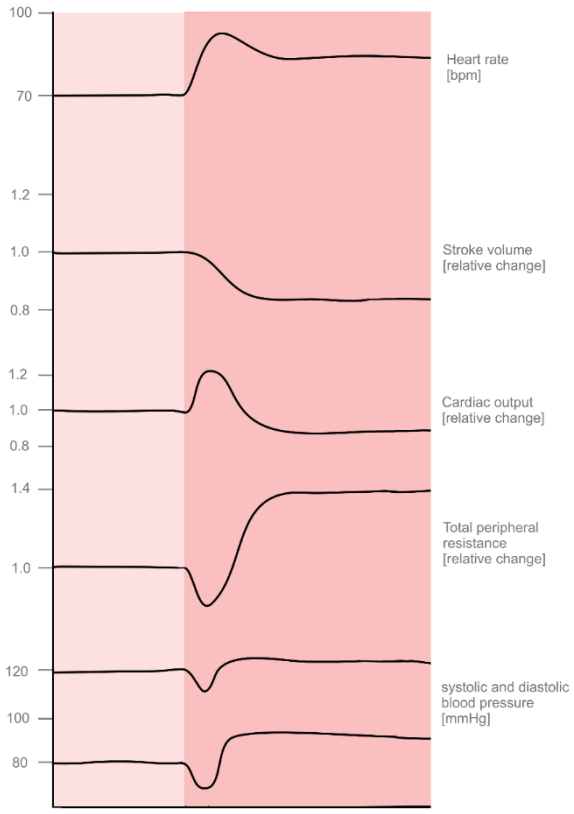


Figure 4:Physiological adaptation to active standing, light red background indicates supine position, darker red background indicates active standing, very rapid alterations during the transition period are intentionally not displayed to correspond to the protocol applied in this thesis, Illustration by the author using information from (3, 4, 7, 11, 19)

slightly lower than that seen in during HUT.(19) The humoral systems, activated by hypotension and increased sympathetic activity during prolonged standing, increase salt and water retention to elevate the circulating blood volume. This is achieved by recruiting the renin-angiotensin aldosterone system, increasing antidiuretic hormone secretion and, decreasing the secretion of atrial natriuretic peptide, triggered by a reduction in atrial pressures.(3, 12)

1.3.2. Impairment of orthostatic blood pressure control

The compensatory mechanisms discussed above prevent significant BP changes in healthy individuals in the upright posture. Disturbances of the cardiovascular autonomic control and the resulting inability of the cardiovascular system to maintain hemodynamic homeostasis within these confines during standing, produce distinct entities of orthostatic blood pressure derailments.

1.3.2.1. Orthostatic hypotension

Orthostatic hypotension (OH) occurs when compensatory mechanisms fail to prevent a fall in BP that meets or exceeds 20 mmHg systolic or 10 mmHg diastolic during the initial 3 minutes of standing.(13) In 2018 the ESC added an absolute cut-off in a decrease of SBP to <90 mmHg after standing up, to also detect patients with supine SBP <110 mmHg with a lower absolute but significant relative SBP reduction.(20) OH can be further distinguished into classic OH, described above, initial OH, which refers to a BP nadir of either 40 mmHg SBP or 20 mmHg DBP within 15 seconds of standing or delayed OH, which only occurs after more than 3 minutes of standing.(14) OH can be the result of both structural and functional failings of ANS that result in an excessive reduction of CO upon standing, an inadequate vasoconstriction and TPR adaptation, or both.(13) This is likely due to impairment of baroreflex function, resulting in an insufficient increase in sympathetic outflow to the heart and vasculature, as the baroreceptor plays a primary role in orthostatic hemodynamic adaptation.(21, 22) Baroreflex sensitivity seems to naturally deteriorate to a certain extent with ageing.(23) OH has been related to further reduced baroreflex sensitivity in elderly hypertensives compared to normotensives, which suggests that other factors then age, such as hypertension, result in further baroreceptor function deterioration and by extension, reduced afferent baroreceptor signalling and poorer orthostatic blood pressure control in spite of functional efferent sympathetic activity.(24) If BP drops cannot be countered adequately, and BP falls below the limits of cerebral autoregulatory control, cerebral perfusion deteriorates and may cause symptoms of presyncope and cerebral hypoperfusion like dizziness and

visual disturbances, leading to falls or outright syncope.(9, 25) The prevalence of OH is highly age-dependent, with 18% in those 65 and older and exceed 20% in those over 70 years.(15, 26) Several age-related factors contribute to higher incidence of OH in the elderly. Decreased baroreceptor sensitivity has been touched on earlier. Additionally reduced parasympathetic tone and thus dampened cardio-acceleration to sympathetic stimuli and reduced renal salt and water retention occur in the elderly. This additionally primes the elderly to dehydration, and consequently OH.(27) Cardiac pump failure has also been described as another common cause for OH, due to chronotropic failure, concomitant vascular aging, capacitance vessel dysfunction and impaired cardiac muscle pump function.(21) Reduced diastolic filling of the ventricles due to myocardial non-compliance in elderly individuals further reduces SV when standing reduces preload.(27) Conditions that contribute structural to autonomic failure such as neurodegenerative disorders, Parkinson's disease, peripheral neuropathies and diabetes also show a high incidence of OH.(27) OH has been identified as an independent predictor for the development of cardiovascular diseases such as coronary artery disease, atrial fibrillation, stroke and heart failure and is predictive of all-cause mortality.(14, 15)

1.3.2.2. Orthostatic hypertension

Orthostatic hypertension (OHT) serves as a contrast to OH, namely a paradoxical increase of BP upon standing, and is also indicative of disturbances of the cardiovascular autonomic control.(28) Compared to OH, OHT is scientifically and clinically underappreciated, not well understood or broadly recognized, but carries important clinical implications due to its prevalence and potential detrimental health consequences.(29) The lack of a universal, agreed-upon definition for OHT hinders scientific inquiry. Recently, experts suggested a sustained increase of ≥20 mmHg SBP above supine levels and/or an increase above 140/90 mmHg from normotensive baseline values for an active stand test as diagnostic thresholds.(30) DBP changes are currently not given any weight in the description of OHT, as DBP increases physiologically during standing on account of peripheral vasoconstriction.(28) The threshold of 20 mmHg was chosen after it was demonstrated, that an increase of 20 mmHg SBP was associated with target-organ damage, though no existing definition is grounded in cardiovascular risk.(28, 31) The underlying mechanisms of OHT are currently not well understood. Early pathogenetic used DBP as a defining threshold and found that the shift from a supine to a standing position incurred a greater reduction in CO, more excessive venous pooling in the legs and higher NE levels after standing up in patients, which were denoted

to have OHT.(32) A lower body pressure suite inflation averted CO reductions and normalized blood pressure response.(32) Kario et al. (2002) corroborated these findings, showing higher levels of supine NE levels, higher NE levels after tilting, as well as higher ADH level after tilting in patients with OHT. It was further demonstrated that the hypertensive response to standing was ameliorated by pharmacological α-adrenergic blockade.(33) It was deduced that OHT may be triggered sympathetic overactivation and excessive peripheral constriction mediated by arterial and cardiopulmonary baroreceptors which are stimulated due to excessive venous pooling and a substantial reduction of CO.(28, 31) Hyperreactivity to α-adrenergic stimulation in the vasculature appears to also play a role, as the blockade of these receptors seems to prevent hypertensive orthostatic responses.(31) OHT has been associated with a wide array of cardiovascular diseases and is more prevalent in patients with higher age, higher BMI, diabetes and hypertension.(28) Extreme nocturnal dipping and morning blood pressure surges in 24h blood pressure measurements were also associated with OHT, which might also point to the sympathetic mediation of the condition.(28, 31) In patients with OHT and OH silent cerebral infarcts and greater individual blood pressure variability were more common than in normotensives. The OHT group had higher rates of left ventricular hypertrophy (LVH) assessed by ECG.(33) Further associations with peripheral artery disease (PAD), stroke and higher levels of cardiac troponin, NT-pro-BNP and carotid plaques have been observed.(34, 35) Higher all cause and cardiovascular mortality in the elderly have been described.(36, 37) Some associations remain unclear in light of the lack of a universal definition of OHT.(38)

1.4. Coronary artery disease

1.4.1. Definition and features

Coronary artery disease (CAD) refers to the obstructive or non-obstructive pathological atherosclerotic plaque accumulation in the epicardial arteries.(39) Ischemic heart disease (IHD), is a condition of myocardial hypoxia, that arises from the imbalance between myocardial oxygen demand and supply, and is most commonly caused by the atherosclerotic narrowing of the coronary arteries.(8) Myocardial ischemia causes angina pectoris, an uncomfortable sensation in the chest, due to the accumulation of waste metabolites and activation of pain receptors.(8) Typical angina causes chest discomfort, often described as pressure, that may radiate to the lower jaw, arm, epigastrium and upper back. It is of relatively short duration (<10 min), with exacerbations in the morning or during exertion, and is relieved upon rest

or nitrate application.(39) CAD can remain stable over prolonged periods, presenting as a chronic coronary syndrome (CCS), but may deteriorate acutely due to plaque ruptures, causing atherothrombotic events which present as acute coronary syndromes (ACS), or result in ischemic heart failure due to chronic IHD.(39, 40) The risk of death in patients with CAD is directly related to its severity and stenosis localization, with higher risk in more extensive coronary disease burden.(40) The global prevalence of CAD has steadily increased, with IHD accounting for nearly 50% of all cardiovascular deaths.(41)

1.4.2. Pathogenesis

Atherosclerosis is a chronic immunoinflammatory disease that primarily affects the large and-medium sized arteries and acts as the underlying cause of CAD development. Endothelial dysfunction precipitates the extravasation of lipoproteins and allows the aggregation and consequent death of foam-cells, immigrated macrophages that internalize and oxidize lipoproteins. This results in the buildup of lipid rich plaque cores. Migrating smooth muscle cells produce a localized fibroproliferation, that can stabilize plaques and prevent ruptures. (42) Expansive arterial wall remodeling usually attenuates the narrowing effect of plaque build-up. Further plaque growth and vessel shrinkage can thereafter result in the development of stenosis and compromise blood flow as is typical in CCS.(43)

1.4.3. Pathophysiology

The plaque build-up and narrowing of the arteries in CAD causes a fixed vessel stenosis and endothelial dysfunction. The results are an increase in vascular resistance due to the stenotic lesions and an abnormal vascular tone.(2, 8) The capability of the distal vessels to compensate through vasodilation for the increased proximal resistance dictates the hemodynamic significance of the stenosis.(3) A narrowing of ~70% will only allow adequate blood flow at rest with maximal distal dilation, but not under exertion, when the proximal stenosis will dominate total resistance.(3) A 90% stenosis will likely compromise blood flow and induce ischemia at rest.(8) The presence of clinical or even subclinical degrees of atherosclerosis additionally impairs endothelial function, resulting in an inadequate release of vasodilating mediators. Consequently functional sympatholysis is impaired and sympathetic vasoconstrictive effects are more dominant.(2, 8) If CBF cannot be increased according to the tissue's metabolic needs, the oxygen supply/demand-ratio is lowered. This results in myocardial ischemia under exertion or at rest, and impairs contraction and diastolic relaxation.(2)

The ensuing increase in LV diastolic pressure is transmitted to the pulmonary circulation and causes pulmonary congestion and dyspnea.(8)

1.4.4. Treatment

Treatment of CAD aims at stabilizing the disease, improving symptoms, preventing progression and myocardial infarction, and improving survival, by implementation of lifestyle modifications, pharmacological treatments, and revascularization procedures. (3, 8, 39) Patients whose symptoms persist despite optimal medical therapy can benefit from coronary revascularization, as it has been shown to improve quality of life and exercise capacity. It can also improve prognosis in patients with left main disease, proximal LAD stenosis, extensive two- or three-vessel disease, an ischemic area >10% of the left ventricular wall, as well as in patients with a single remaining coronary artery with >50% stenosis.(44) The revascularization can be achieved by coronary artery bypass graft (CABG) surgery during which arterial or superficial venous vessels are grafted from the aorta or subclavian artery to a site distal of a coronary stenosis. This allows blood flow to circumnavigate the stenotic lesion and improves perfusion of the downstream vasculature. The procedure is most commonly conducted after sternotomy as on-pump CABG during extracorporeal circulation on a cardioplegic heart.(8) Alternatively percutaneous coronary intervention (PCI) allows for minimally invasive transluminal coronary angioplasty and coronary stent implantation by inserting a catheter into the coronary arteries, obtaining radiographic anatomical imaging and dilating isolated stenoses with balloon-catheters.(8) Between CABG and PCI, CABG should be preferred in patients with higher complexity multi-vessel disease, in the presence of diabetes, impaired LV-function, recurrent stenosis and contraindications for dual antithrombotic treatment, and when other cardiac surgery is necessary. On the other hand, PCI is generally preferrable in older, frail patients with high surgical risk, severe comorbidities and limited life expectancy and lower complexity of coronary stenosis anatomy.(44) CABG has been shown repeatedly to improve quality of life, increase life expectancy and, arguably through ‘surgical collateralization’, prevent myocardial infarction in patients with stable CAD, while PCI has yet to demonstrated survival benefits or a reduction of myocardial infarction in stable CAD.(40)

1.4.5. Hemodynamic postural control and CAD

As has been laid out in Chapter 1.3. the maintenance of orthostatic tolerance is dependent on the successful integration of autonomic, cardiac, vascular and humoral control mechanisms to preserve postural homeostasis. Orthostatic intolerance syndromes occur as an expression of the disturbance of the explored control mechanisms, chiefly cardiovascular autonomic dysfunction or sympathetic failure. The chief mechanism of initial BP stabilization during orthostasis is the baroreceptor reflex. It is well established that Baroreflex function worsens with age and due to hypertension and atherosclerosis.(45) As mentioned above, lower baroreceptor-heart rate reflex sensitivity has been related to orthostatic falls in systolic blood pressure in elderly hypertensives.(24) In patients with asymptomatic CAD and stable, meaning symptomatic CAD, baroreflex sensitivity has been shown to be impaired. The severity of baroreflex impairment is associated with the extent and severity of the coronary disease burden, independent of prior myocardial infarction (MI).(46, 47) The impairment of baroreflex function may therefore lead to higher incidence of postural hypotension in vascular disease and the elderly.(45) Autonomic modulation of the heart and blood vessels, assessed by blood pressure and heart rate variability (HRV) is also impaired in patients with stable CAD with no history of MI to the same extent as in patients with chronic heart failure.(48) Impairment of cardiac autonomic function, assessed by HRV, and an increased risk of developing CAD have been associated in the ARIC study.(49) The relationship between postural blood pressure variability and CAD has been further corroborated by the fact, that postural hypotension in itself represents an independent risk factor for the development of CAD, future coronary events and cardiovascular mortality, which has been demonstrated in multiple observational trials.(35, 50, 51) Also, in patients with OH higher levels of circulating atherothrombotic and inflammation markers have been observed, which may promote cardiovascular disease progression.(52) One cannot infer a causal relationship between the presence OH and the development of CAD from observational trials. OH may very well be a surrogate of altered autonomic and vascular properties in subclinical atherosclerosis and consequently impaired sympathetically mediated vasoconstriction and heart rate adaptation to postural stressors.(35, 53) These findings suggests, that cardiovascular autonomic dysfunction and possible impairments of hemodynamic postural control do not only predate cardiovascular disease, but may also be present in patients with established CAD.

1.5. Aortic stenosis

Aortic stenosis (AS) is defined as the obstruction of the semilunar aortic valve opening, that leads to the development of a pressure gradient between left ventricular outflow tract and the aorta.(54) AS accounts for the majority of valvular heart diseases and is most common in the elderly population with a 2% prevalence in patients older than 65 years, which rises to 4% in patients older than 85 years.(55) Its incipient stage, aortic valve sclerosis, is present in 26% of patients >65 years and increases to up to 48% of patients > 85 years of age.(56) Isolated aortic stenosis is most commonly symptomatic and classified as severe once the aortic valve opening area falls below 1,0 cm^2, the transaortic jet velocity surpasses 4,0 m/s and the transvalvular pressure gradient exceeds 40 mmHg (Figure 5).(57) The presence of severe aortic stenosis indicates worsening survival evidenced by a 2-year mortality of 50% if not treated, even in asymptomatic patients.(58)

1.5.1. Pathogenesis

Calcific aortic valve stenosis accounts for 82% of all aortic valve stenoses and is thereby the most common form. It presents with calcium deposits within the central and basal parts of the aortic cusps (Figure 5). (54, 56, 59, 60) Atherosclerosis and AS share associated risk factors and often coincide in the same individuals, which might be suggestive of a common pathogenesis.(41, 56, 61, 62) Other causes may be rheumatic valve disease or congenital bicuspid valves.(56)

1.5.3. Pathophysiology

Aortic valve narrowing below 1,5 cm^2 strains the left ventricle by increasing afterload and escalating systolic intraventricular pressures.(8) The loss of the blood's kinetic energy along the stenosis incurs a pressure gradient, that is dependent on the degree of narrowing and flow (Figure 5).(2) The increase in afterload causes a reduction of SV and thus increase end-systolic volume, which needs to be offset by increasing contractility in accordance with the Frank-Starling mechanism to maintain CO.(2, 8) To compensate for the progressively increasing wall-stress, the left ventricle's walls need to thicken, which results in concentric LVH.(56, 57, 63) This mechanism is paramount in overcoming the heightened afterload and maintain systolic ejection but comes at the price of impaired coronary blood-flow during diastole. Myocardial oxygen demand is increased by higher muscle mass and elevated wall stress. Higher diastolic pressures, which reduce perfusion pressure in the coronary arteries, and shorter diastolic filling time reduce oxygen supply and may lead to the development of

angina, especially during exertion.(3, 8, 57) LVH hinders passive filling of the ventricles during diastole due to reduced compliance of the ventricle walls and ventricular remodelling. Thus elevated diastolic pressures to expand the thickened myocardium are required.(8)

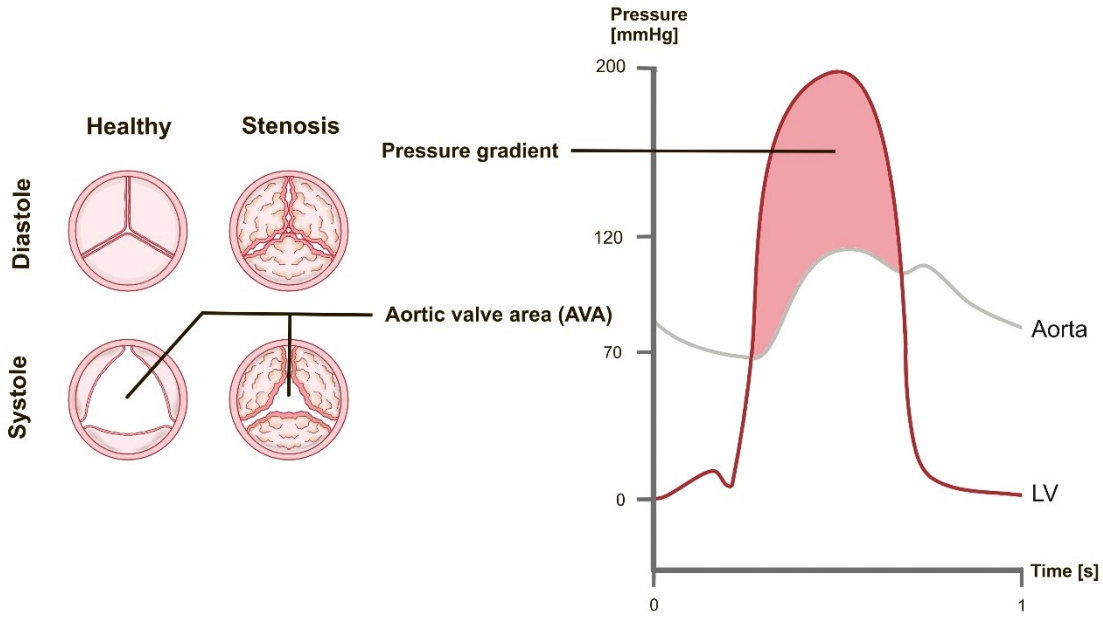


Figure 5: Illustration of a healthy and stenotic aortic valve (degenerative) with calcific deposits during the cardiac cycle. Pressure-time diagram in the presence of aortic stenosis. A reduction in AVA incurs a pressure gradient between left ventricle (LV) and the ascending aorta during systole, and delays ascend of the aortic pressure curve, Illustration by the author using information provided in (2, 3, 8)

The increase in end-diastolic pressures facilitates hypertrophy of the atrium to maintain active filling of the ventricle and causes atrial enlargement. In the long-term, progressive narrowing of the aortic valve leads to the deterioration of the contractile function, further increasing diastolic volume and pressure. The elevated diastolic pressures are transmitted into the pulmonary veins, cause pulmonary congestion and result in symptoms of heart failure, such as dyspnoea.(8, 56, 57) During exercise CO should rise to keep blood pressure high and ensure stable cerebral perfusion when TPR falls due to skeletal muscle activation and the ensuing peripheral vasodilation. Syncope during exercise in aortic stenosis patients could arise because of the narrowing of the AVA and the reduction in ventricular filling time, resulting in a limitation of CO as is described by the Frank-Starling mechanism.(8)

1.5.4. Treatment

The only means of improving survival and morbidity in AS is either surgical aortic valve replacement (SAVR) or the more recently established transcatheter aortic valve replacement (TAVR). It has long-since been established that SAVR significantly improves survival in patients with symptomatic severe AS compared to conservative management.(64) SAVR remains the standard approach for all symptomatic patients with low surgical risk and should be considered in symptomatic patients with intermediate surgical risk in accordance with the heart team decision and individual patient characteristics.(62) TAVR is a catheter based technique, which allows balloon- or self-expanding biological valves to be placed in, and displace the stenotic valve without its removal and without open heart surgery. It has initially emerged as a minimally invasive alternative to SAVR in patients who were deemed ineligible for surgery or have high surgical risk and has since expanded to be a viable alternative for patients with intermediate surgical risk. While it is less invasive than open heart surgery, it comes with its own set of possible complications and long-term data of valve survival are still lacking. (62)

1.5.5. AS and its implications for orthostatic blood pressure control

AS has not been commonly associated with orthostatic blood pressure dysregulations, but reactions to orthostatic stress in patients with AS have also not been studied extensively. Several features of AS and its concomitant conditions might pose challenges to orthostatic control. Some authors proposed the possibility that the fixed obstruction of the outflow tract limits the adaptation of CO in patients with AS during orthostasis, thus aggravating cerebral perfusion.(65) A recent study found that in elderly patients with severe AS and impaired LVEF, both CO and brain perfusion, assessed by gas rebreathing and MRI respectively, improved after TAVR.(66) This lends more credibility to the hypothesis that in patients with AS and impaired LV function, brain perfusion may be impaired even at baseline, and may therefore deteriorate during orthostasis. Indeed some research suggest that in patients with AS, higher carotid and vertebral flow velocity drops, and reductions in transvalvular gradients during orthostatic stress can be observed than in healthy controls.(67, 68) In a follow-up study, the drops in flow velocity seemed to coincide with a history of syncope, though not in the original study.(69) Thus, the clinical importance of this finding remains questionable. The authors suggest, that in patients with severe AS, SV might be reduced even in the case of normal EF and thus limit cerebral blood flow upon orthostatic preload restriction and further SV attenuation. In another follow-up study, flow velocity and volume was remedied

after TAVR, thereby possibly improving cerebral perfusion and reinforcing the causal relationship to the presence of AS.(70) Furthermore, some degree of autonomic dysfunction seems to be prevalent in patients with AS. Increased sympathetic drive, assessed by HRV, seems to be highly prevalent in patients with AS, which is suggested to normalize after valve replacement.(71) The increased sympathetic drive has also been demonstrated in children, which may detract from a possible age-dependency and may point to a connection with the underlying cardiac pathology.(72) AS patients have been shown to have dampened cardiac parasympathetic responses in the supine position and showed reduced autonomic adjustments to active standing compared to healthy controls.(73) Conversely cardiac sympathetic nervous overactivation has been found in AS, and has been shown to improve after TAVR.(74) Increased general sympathetic nervous system activity, assessed by muscle sympathetic nerve activity (MSNA), and reduced spontaneous sympathetic baroreflex gain were found in patients with AS and have been demonstrated to be improved after TAVR. Increased sympathetic activity has been related to decreased cardiac index, higher LV volume and LVH in this study. The higher sympathetic activity has been hypothesized to be related to reduced afferent baroreceptor activity, as baroreceptor gain was lower in AS patients before and higher after TAVR, which coincides with the reduction in sympathetic activity after the intervention.(75) Sympathovagale imbalance, assessed by HRV and heart rate turbulence (HRT), indices of autonomic dysfunction and marker of baroreceptor sensitivity, was disturbed in patients with AS and was related to diastolic dysfunction in AS.(76) As previously explored, diastolic dysfunction is naturally connected to AS disease progression and the ensuing LVH. In patients with moderate to severe AS, severe autonomic failure assessed by HRT was found in 25% and was associated with lower EF, lower valve gradients, higher pulmonary pressures and signs of HF.(77) Severe autonomic failure was also highly predictive of mortality after AVR in both previously symptomatic and asymptomatic patients.(78) The pathophysiology and findings, presented above, suggest that structural as well as functional changes to the cardiovascular and autonomic nervous system control mechanisms occur in the presence of AS, that may pose challenges to orthostatic hemodynamic control.

2. Aims and Objectives

As was laid out previously, the presence of CAD and AS confer a wide array of structural and functional changes to the autonomic cardiovascular control mechanisms as well as the cardiovascular anatomy and physiology themselves. These alterations could challenge postural hemodynamic homeostasis. As presented in Chapters 1.4 and 1.5, both CAD and AS are often associated with alterations of autonomic heart rate control, indicative of overall autonomic dysfunction. Strong connections exist between reduced baroreflex sensitivity, which has been related to orthostatic blood pressure falls in the elderly, and CAD disease burden. Furthermore, an inverse relationship between CAD and OH has already been described in large epidemiological studies, with OH predating the development of CAD, possibly due to general atherosclerotic and inflammatory disease burden.

AS seems to be pose structural challenges to blood pressure control, in the sense of additively increased LV afterload and thus induced cardiac remodeling and is often accompanied by coexisting hypertension and diastolic dysfunction. It is connected to an increase in both cardiac and overall sympathetic activation as well as impaired autonomic adjustments upon standing. Spontaneous baroreflex gain seems to also be reduced in patients with AS but has not been studied under orthostatic challenge. A reduction in cerebral perfusion both in a supine position and exaggerated cerebral flow reductions during shifting into an upright position have also been demonstrated.

In light of the challenges posed by both conditions, we hypothesize that:

1. Orthostatic hemodynamic response is impaired in patients with AS and CAD.
2. Orthostatic hemodynamic responses differ between patients with AS and patients with CAD.

This thesis aims to explore these hypotheses as part of the pilot study “Effects of plantar vibration on early postoperative mobilization of patients undergoing heart surgery (Cardio-Vib)”.

3. Methods

3.1 Study design

This thesis was conducted as part of the CardioVib pilot-study, a collaborative trial between the departments of Physiology and Heart Surgery of the Medical University of Graz. The CardioVib study was designed as a prospective randomized controlled trial, which assessed the effect of a plantar vibration plate on cardio-postural control in patients undergoing heart surgery, using a supine-to-stand test to induce orthostatic stress.

The study aimed to randomized 30 participants, who underwent either SAVR or CABG, into three cohorts with 10 subjects each, irrespective of the underlying pathology, and subjected them to different postoperative intervention protocols. The postoperative protocol encompassed either plantar vibration and partial weight loading, partial weight loading alone by tilting of the bed for 15 minutes per day, or standard postoperative care.

For this thesis, we grouped patients according to the underlying heart condition in an AS and CAD group and compared the hemodynamic changes during the supine-to-stand test, which were conducted before surgery. At this time no intervention had taken place. For the purpose of this thesis, only hemodynamic monitoring data are utilized. No healthy control group was included in the CardioVib trial. Thus, the null hypothesis of hemodynamic competency would be rejected under the condition that overt orthostatic blood pressure dysregulations in the aggregate of each group were present. The null hypothesis of no difference in hemodynamic reaction to orthostatic stress would be rejected on the basis of significant interaction effects between groups in the statistical analysis of the hemodynamic monitoring data.

3.2 Ethical approval

The ethical board of the Medical University of Graz (Graz, Austria), where the CardioVib study was conducted, approved of the study's research protocol and subsequent changes to it (EK-number: 31-343 ex 18/19). The trial was performed in accordance with the standards laid out by the Declaration of Helsinki and registered on clinicaltrials.gov (NCT-number: NCT04243213).

3.3 Recruitment

The study was carried out at the Department of Heart Surgery at the Medical University of Graz. Patients had to fulfil the following eligibility criteria, as per the study's protocol and trials.gov:

Inclusion criteria:

65 - 85-years-old, undergoing conventional aortic valve replacement surgery or coronary artery bypass graft surgery

Exclusion criteria:

- Euroscore II > 8
- Postoperative delirium upon 48h after surgery, requiring medicinal treatment
- High dose catecholamine support 48h after surgery
- Existing thrombosis

Participants were recruited from September 2019 to June 2021. Recruitment of the subjects, including suitability evaluation and medical history review, was conducted by the Department of Heart Surgery. All participants were informed of their right to terminate their participation in the study at any time and without any reason. The study's protocol and measurements were explained to each patient and signed consent forms were obtained and stored.

3.4 Protocol

The participants underwent a 15-minute supine-to-stand test to induce orthostatic stress, whilst under extensive hemodynamic monitoring. After a 5 minute supine resting period and Baseline measurement, subjects were asked to stand up without a prior countdown, to keep their eyes open and fixated on a point at eye level, and to remain standing on the same spot on a pressure plate. After 5 minutes of standing, return to the supine position for another 5 minutes of recovery was conducted (see Figure 6). Supine-to-stand tests were chosen over sit-to-stand test due to the latter's poor sensitivity and specificity for diagnosing orthostatic blood pressure disturbances.(79) Current guidelines and publications recommend supine-to-stand tests for the diagnosis of OH and OHT respectively.(20, 30) Additionally a supine starting position was thought to be more tolerable for patients after surgery. Tilt-testing, induces different hemodynamic stimuli and could not be performed on patients mere days after surgery.(25).

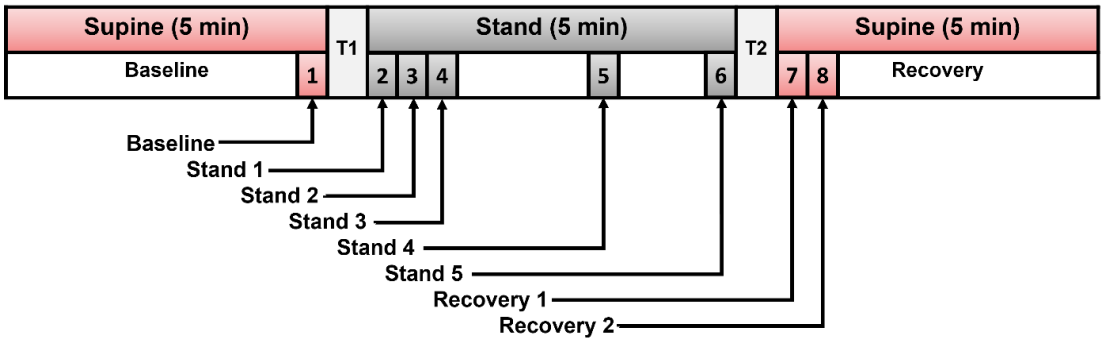


Figure 6: Supine-to-stand-(to-supine)-protocol, squares 1-8 represent the 10s epochs and their corresponding designation, position changes are marked as transition periods (T1 and T2) 1 epoch ≙ 10 second interval

10 second spot samples, named epochs, which represent time points of interest during the supine-to-stand protocol, were identified and used for the further analysis. The experimental protocol and epochs used in this analysis, as well as their corresponding timeframes in the protocol are elucidated in the Table 1 and Figure 6. Times needed for the completion of the posture change were marked as transition times in the monitoring to be differentiated and excluded from the analysis

Table 1: Supine-to-Stand protocol – epochs, corresponding designation and description

Epoch	Corresponding spot	Description
Epoch 1	Baseline	Last 10 seconds of the baseline supine position
Epoch 2	Stand 1	First 10 seconds of stand
Epoch 3	Stand 2	Second 10 seconds of stand
Epoch 4	Stand 3	Third 10 seconds of stand
Epoch 5	Stand 4	10 seconds between 180 and 190s of stand
Epoch 6	Stand 5	Last 10 seconds of stand
Epoch 7	Recovery 1	First 10 seconds after return to supine
Epoch 8	Recovery 2	Second 10 seconds after return to supine

3.5 Setting

Measurements and interventions were performed between 8 am and 1 pm and took place either on the ward of the heart surgery department or the postoperative surveillance and intensive care units (ICU). All participants were asked to report discomfort or dizziness and to sit down, should such early signs of syncope occur.

Safety precautions such as assistance in standing, constant hemodynamic monitoring and attendance by medical professionals were taken to avoid falls and injuries from syncope or OI.

3.6 Measurements

The Task Force® Monitor (TFM), a non-invasive device to measure, display, record and extrapolate hemodynamic parameters in real-time, was used to conduct a continuous hemodynamic and autonomic monitoring for the duration of the protocol. The monitoring combines intermittent oscillometric and continuous beat-to-beat blood pressure measurement by finger plethysmography. Intermittent blood pressure measurements on the left arm were run to calibrate the continuous beat-to-beat measurement, attached to the right forearm, which is constantly being held at heart level by an arm sling while standing (Figure 8). Finger-cuff plethysmography is well validated against intra-arterial BP measurement and is recommended for OH assessment, especially when rapid, short term blood pressure alterations are observed.(11, 20, 25) SBP and DBP are derived from the finger plethysmograph, while MBP is calculated from SBP and DBP. Continuous thoracic impedance cardiography (ICG) was recorded by four impedance electrodes, three of which were attached to the neck and the lateral sides of the lower thorax, at the level of the diaphragm. Additionally, a 3-lead electrocardiogram (ECG) is continuously recorded in sync with the ICG and BP measurement. The TFM has been validated against other non-invasive hemodynamic monitoring devices for continuous blood pressure and ICG measurements and was deemed substantially equivalent.(80). The TFM calculates SV from changes in the thoracic electrical conductivity measured by the ICG. From SV, HR, MBP and BSA (approximated by DuBois formula) the TFM derives cardiac output, cardiac index, and other cardio dynamic parameters, such as total peripheral resistance and total peripheral resistance index. CO is calculated according to the formula provided in Chapter 1.1 and Figure 7 and divided by BSA to attain CI. TPRI is attained by the formula provided in Figure 7, by dividing with CI, instead of CO.(81)

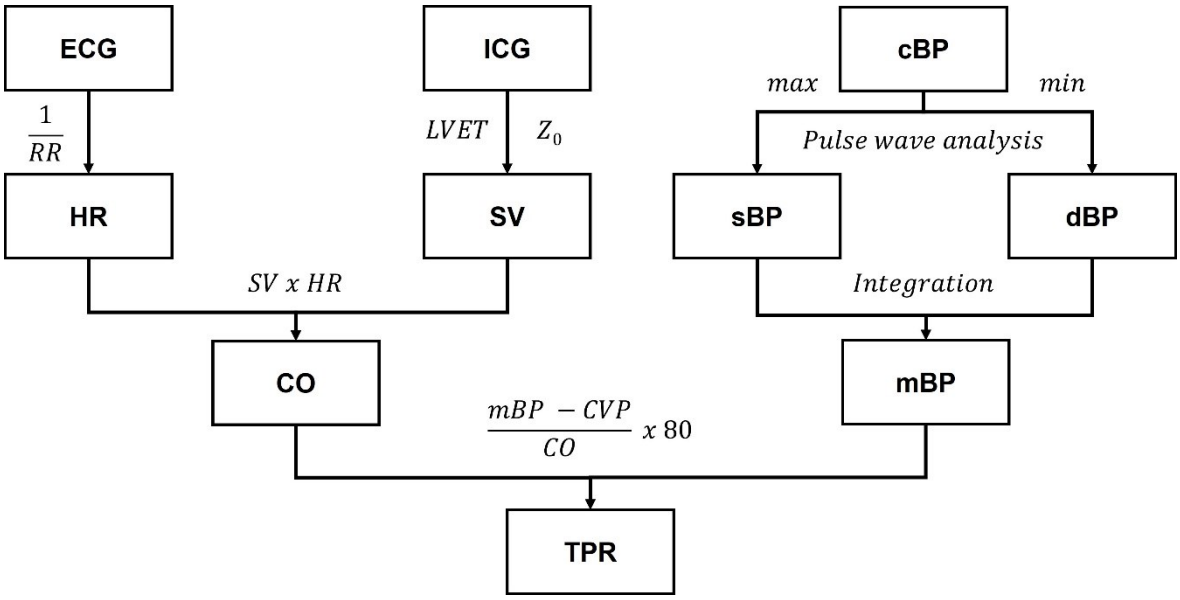


Figure 7: Interdependence and calculation of beat-to-beat TFM parameters. The TFM detects RR-intervals and calculates HR accordingly, from the ICG the TFM detects thoracic impedance changes and ejection time and calculates SV, the continuous blood pressure allows extrapolation of maxima and minima of the finger pulse wave to systolic and diastolic blood pressures. Central venous pressure (CVP) fixed at 3 mmHg by the software. Illustration by the author.

Surface electromyography (EMG) and near infrared spectroscopy (NIRS), attached to the calves, recorded either muscle activity in the supine and standing position or quantify venous pooling respectively. Postural Sway was recorded using force- and movement data from a pressure plate. Orthostatic changes in cerebral blood flow velocity were detected using transcranial doppler (Multiflow, DWL, Sipplingen, Germany) of the mid cerebral artery. Additional ECG leads were attached to the limbs in accordance with the Einthoven's triangle and its signal relayed to the EMG, NIRS and transcranial doppler to synchronize measurements between devices. Groningen Frailty Index-, BDI-II and FES-I questionnaires were conducted before, 7 days after and 3 months after surgery to gauge frailty, severity of depression symptoms, and fall risk. The complete experimental setup is detailed in Figure 8, provided below.

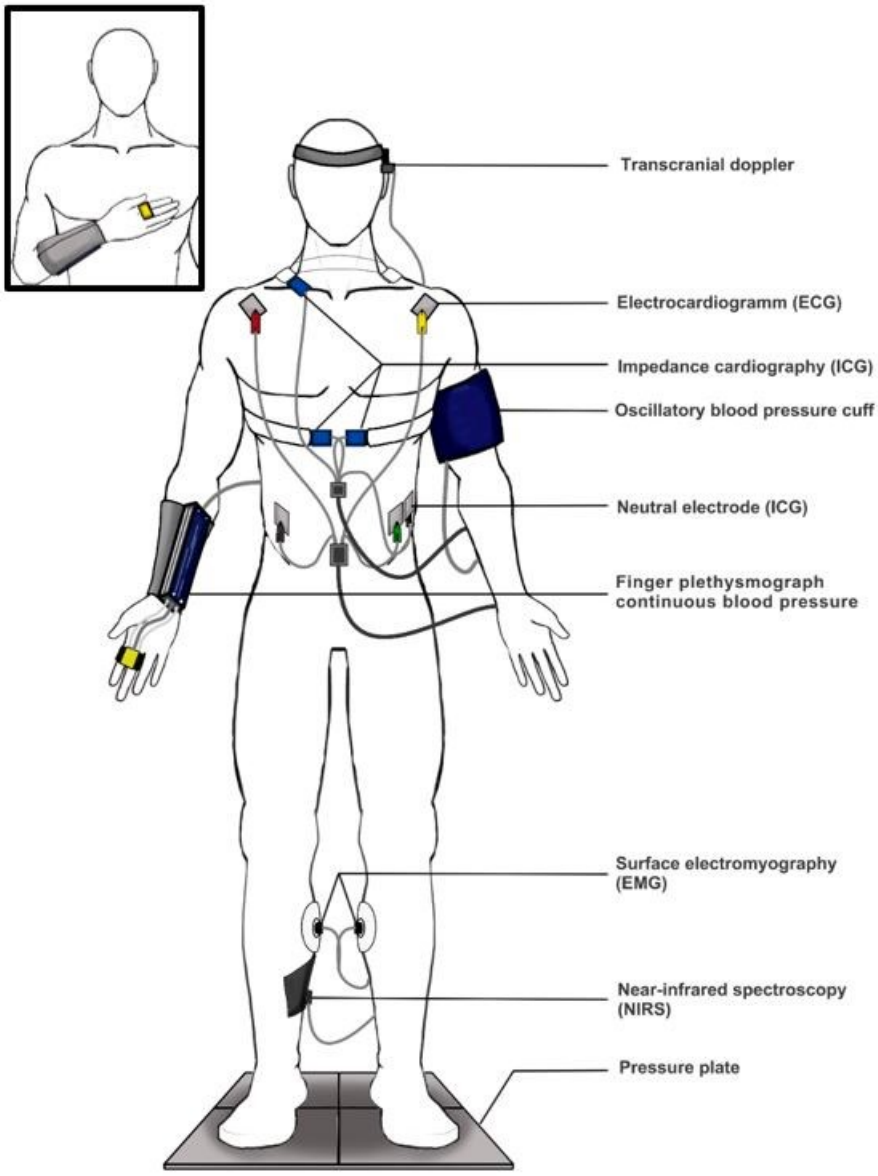


Figure 8: Illustration of the experimental setup, a subject donning the equipment used in the CardioVib study, finger plethysmograph not at heart level in the picture for visibility concerns, upper left corner demonstrates the correct positioning of the cuff at heart level during standing. Additional fixation tapes secure electrodes in place and a sling is attached to the contralateral shoulder to keep the continuous blood pressure cuff at heart level. Illustration by the author.

3.7 Data analysis

Ten second intervals, corresponding to the aforementioned epochs (Figure 6), were averaged for heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), stroke volume (SV), stroke index (SI) cardiac output (CO), cardiac index (CI), total peripheral resistance (TPR) and total peripheral resistance index (TPRI). After inspecting the data available, two patients were removed from further analysis due to

TFM data missing entirely or for the duration of multiple epochs during the recovery period. Extreme outliers ≥3 interquartile ranges were identified using boxplots.

Two extreme outliers in the AST group and 1 outlier in the CAD were identified, that showed abnormally high measurements for SV and CO respectively. From investigating the continuous beat-to-beat data, erroneous measurements seem a likely cause for these abnormal values. As such we removed the values for SV and those calculated from SV, i.e., SI, CO, CI, TPR and TPRI of these patients from further analysis. Since the other parameters (HR, SBP, DBP, MBP) remained unaffected, they were retained in the analysis. One outlier with extreme values for HR during stand was identified in the CAD group, consequently the HR measurements and variables calculated from heart rate (CO, CI, TPR, TPRI) were removed from further analysis. Judging from the beat-to-beat data, either erroneous HR detection or the presence of absolute tachyarrhythmia seem to be the cause of the extreme measurements. In the case of missing data, mean substitution was applied for one subject in the first 10 seconds of standing.

From the 10 second means, we identified those individuals that concurred with the definitions laid out in 1.3 (ΔSBP >20 mmHg). Those identified as hypertensive responders within their respective subgroups were classified as AS OHT and CAD OHT. The definition of orthostatic hypertension provided by Finucane et al defines OHT as a sustained increase of blood pressures, where 'sustained' refers to the timeframe from 60 to 180 seconds after standing up.(30) The epochs used in this study's protocol are not wholly overlapping with the recommended definition, thus the suggested definition cannot be applied to our findings in its entirety. Stand 4 however, corresponds to 180-190s of standing and can be used as a spot-check at 3 minutes. Therefore, Baseline values were subtracted from Stand 4 to gauge the blood pressure response to active standing and the difference was individually inspected to see if the thresholds in the definitions were met under these conditions. Likewise, the definition of OH refers to a sustained drop in BP, thus the same method of spot check comparison was applied to infer if the criteria have been met.(20)

3.8 Statistical analysis

The biometric data and transition times were tested for normal distribution using Shapiro-Wilk test. As all biometric data revealed normal distribution within groups, we conducted an independent sample t-test to assess group differences. Since transition times did not follow normal distribution, we used Mann-Whitney U test to identify group differences. The

distributions between groups, assessed by Kolmogorov-Smirnov test, did not differ significantly ($p>0.05$), thus medians could be compared between groups. The hemodynamic data were exported to, and further analyzed with IBM SPSS Statistics 27.

To test the first hypothesis, we conducted a repeated measures ANOVA with the 8 epochs in each group to assess each group's reaction to the protocol individually. Shapiro-Wilk test was performed for all variables and each epoch to examine the data for normal distribution. In total four violations of normal distribution were detected for: HR stand 4 ($p=0.014$), SBP stand 5 ($p=0.031$), SV stand 3 ($p=0.030$) in the AS group and CI recovery 2 ($p=0.047$) in the CAD group. These deviations from the normal distribution were tolerated due to the ANOVAs inherent robustness against violations of normal distribution. In the case of violation of sphericity, Greenhouse-Geisser correction was applied.

Group differences were tested for using a mixed design ANOVA, using the supine-to-stand test (8 epochs) as the within-subject factor and the underlying heart condition (groups) as the between-subject factor. Lack of sphericity was corrected for, using the Greenhouse-Geisser correction. Homogeneity of the error variances was not violated by HR, SBP, DBP, MBP, CO, TPR and TPRI as assessed by Levene's test. Homogeneity of error variances assessed by Levene's test was severely violated in the case of SV and SI. As such the results of the mixed ANOVA for these parameters were not evaluated and are not reported. The homogeneity of error variances assessed by mean was also violated by CI ($p=0.029$) at stand 2, but not when assessed by median ($p=0.125$), and as such tolerated. The homogeneity of covariances was violated by HR ($p=0.007$), SV ($p=0.006$), SI ($p=0.004$), CO ($p<0.001$) and CI ($p=0.032$) Homogeneity of covariances was established for SBP ($p=0.564$), DBP ($p=0.111$), MBP ($p=0.186$), TPR ($p=0.512$) and TPRI ($p=0.535$).

Biometric data between AS OHT and CAD OHT groups were compared using independent sample t-test. We repeated the 2x2 mixed ANOVA for the AS OHT and CAD OHT group for CI and TPRI, after testing for normal distribution using Shapiro-Wilk-test. Normal distribution was violated by TPRI at baseline ($p= 0.036$) and CI at stand 4 ($p=0.005$) in the AS OHT group. An outlier with high CI values was identified in the ASOHT group, but as no suspicion of measurement errors arose, remained in the analysis. Homogeneity of error variance was not violated, and homogeneity of covariances was confirmed by Box's M test. A p-value < 0.05 was interpreted as statistically significant.

4. Results

4.1 Group characteristics

A total of 23 patients admitted to the LKH Graz for elective cardiac surgery, which were enrolled into the Cardio-Vib study. Subjects were assigned to one of two groups based on their primary underlying heart condition that required cardiac surgery.

One group was made up of patients with severe and/or symptomatic aortic stenosis (AS), that required biological or mechanical valve replacement, the other comprised patients with varying degrees of coronary artery disease (CAD) that underwent coronary artery bypass graft surgery. The AS group included 11 patients, 6 male and 5 female. One patient in the AS group additionally suffered from relevant CAD and consequently underwent combined surgery. It was determined by the enrolling physicians, that the primary reason for admittance to surgery was the aortic valve. The 12 patients that were designated to the CAD group, were all male. One subject in the CAD group additionally underwent surgical repair for a patent foramen ovale. Mean age of the groups were 72 ± 6.33 (AS) and 67 ± 5.65 (CAD) years respectively. The difference did not reach statistical significance. Mean bodyweight, height, BMI and BSA did not differ significantly between groups (see Table 2).

Table 2: Group characteristics of subjects in the AS and CAD group

	AS	**CAD**
n	11	12
Male	6	12
Female	5	0
Age [y]	71.9 ± 6.3	67.1 ± 5.7
Weight [kg]	78.1 ± 8.1	81.6 ± 13.7
Height [cm]	168.5 ± 9.8	175.6 ± 5.4
BMI [kg/m²]	27.67 ± 3.74	26.4 ± 3.8
BSA [m²]	1.88 ± 0.13	1.97 ± 0.17

Values expressed as mean ± standard deviation

There was a significant difference of the median transition time from supine to stand (T1) between groups. No significant difference in the median transition time from stand back to supine (T2) between groups was observed.

Table 3: Mann-Whitney U test for transition times between groups

	AS	CAD	Mann-Whitney U test exact significance (2-way)
N	11	12	
T1 Median [s]	55.5*	24.1*	**U=23.00, Z=-2.646, p=0.007, r=-0.552**
T2 Median [s]	24.4	16.5	U=38.00, Z=-1.724, p=0.088, r=-0.359

*statistically significant p<0.05

4.2 Hemodynamic response to active standing within groups

Statistical analysis for all hemodynamic parameters was conducted. The results of SV, CO and TPR are largely omitted from the results section, as they add little informative value over their indices and lack their inherent standardization for body composition. The results for these values are provided in the supplement (Chapter 8). The results of the repeated measures ANOVAs (rmANOVA) are reported in Table 4 below. In both groups, the protocol induced statistically significant changes with the exception of SBP in the CAD group.

Table 4: Results of the repeated measures ANOVA for the AS and CAD groups respectively

Group	Parameter	n	Result – repeated measures ANOVA (8 epochs)
AS	**HR****	11	F(2.916, 29.156)=10.744, p<0.001, η2=0.518
	SBP*	11	F(2.403,24.032)=6,673, p=0.003, η2=0.400
	DBP**	11	F(2.024,20.238)=16.200, p<0.001, η2=0.618
	MBP**	11	F(2.272, 22.716)=12.228, p<0.001, η2=0.550
	SI*	9	F(1.713, 17.067)=10.17, p=0.003, η2=0.560
	CI*	9	F(2.289, 18.312)=6.618, p=0.005, η2=0.453
	TPRI**	9	F(2.287, 18.295)=14.473, p<0.001, η2=0.644
CAD	**HR***	11	F(2.944,29.443)=7.010, p=0.001, η2=0.412
	SBP	12	F(3.070,33.770)=2.121, p=0.115, η2=0.162
	DBP**	12	F(2360, 25.955)=13.276, p<0.001, η2=0.547
	MBP*	12	F(2.683, 29.509)=7.341, p=0.001, η2=0.400
	SI*	11	F(1.878, 18.779)=5.7, p=0.013, η2=0.363
	CI*	10	F(2.698, 24.284)=6.014, p=0.004, η2=0.401
	TPRI**	10	F(2.830, 25.474)=8.041, p<0.001, η2=0.472

*statistically significant p<0.05
**highly statistically significant p<0.001

Following the rmANOVA, we conducted the mixed ANOVA with epochs as the within-subject factor and the underlying heart condition (group either AS or CAD) as the between-subject factor. The results are reported below in Table. 5.

As was to be expected from the significant results of the repeated measures ANOVA, there was a significant main effect of epochs for all parameters. A significant main effect for group was found for TPRI, as well as a trend (p=0.072) for CI. No significant interaction-effect was observed for any of the hemodynamic parameters, which suggests that, despite significant group differences, the reaction to the supine-to-stand protocol was not significantly different between groups. The mean values for each epoch and group are reported in Table 6.

Table 5: Results of the mixed ANOVA – 8 epochs, 2 groups

Parameter	n total	Factor	Result – mixed ANOVA
HR	22	**Epochs****	F(3.371, 67.411)=15.768, p<0.001, η2=0.441
		Group	F(1,20)=0.131, p=0.721, η2=0.007
		Epochs x Group	F(3.371, 67.411)=1.941, p=0.124, η2=0.088
SBP	23	**Epochs****	F(3.126, 65.639)= 7.680, p<0.001, η2=0.268
		Group	F(1,21)=0.706, p=0.410, η2=0.033
		Epochs x Group	F(3.126, 65.639)= 1.237, p=0.286, η2=0.056
DBP	23	**Epochs****	F(2.449,51.429)=28.782, p<0.001, η2=0.578
		Group	F(1,21)=0.823, p=0.374, η2=0.038
		Epochs x Group	F(2.449,51.429)=0.869, p=0.444, η2=0.040
MBP	23	**Epochs****	F(2.796, 58.711)=18.688, p<0.001. η2=0.471
		Group	F(1,21)=0.912, p=0.350, η2=0.42
		Epochs x Group	F(2.796, 58.711)=1.103, p=0.353, η2=0.050
CI	19	**Epochs****	F(2.736,46.518)=12.165, p<0.001, η2=0.417
		Group	F(1,17)=3.686, p=0.072, η2=0.178
		Epochs x Group	F(2.736,46.518)=0.211, p=0.872, η2=0.012
TPRI	19	**Epochs****	F(3.289,55.917)=21.769, p<0.001, η2=0.562
		Group*	F(1,17)=8.127, p=0.011, η2=0.323
		Epochs x Group	F(3.289,55.917)=21.769, p=0.237, η2=0.078

*statistically significant p<0.05
**highly statistically significant p<0.001

Table 6: Group mean values ± standard deviation of hemodynamic parameters over the course of the supine-to-stand protocol

			Means of hemodynamic parameters							
			Baseline	**Stand**					**Recovery**	
Parameter	**Group**	**N**	**Epoch 1**	**Epoch 2**	**Epoch 3**	**Epoch 4**	**Epoch 5**	**Epoch 6**	**Epoch 7**	**Epoch 8**
HR	AS	11	62.9±10.2	**76.5±11.4***	72.8±14.1	72.8±14	71.8±13.5	72.3±14.4	69.5±12.2	63.4±10.1
[bpm]	CAD	11	60.4±9.8	**72.9±9.3***	**70.3±8.7***	**69.9±8.1***	67.6±9.5	69±7.7	**72.2±15***	**66.7±11.5***
SBP	AS	11	113±15.6	127.6±16.1	133.3±19.4	128.8±20	**135.3±15.9***	**135.6±18***	120.2±24.5	118±23.4
[mmHg]	CAD	12	113.8±14.8	122.2±22.5	123.7±22.9	124.1±23.7	126.6± 20.7	121.2±21	114.1±16.2	118.6±17.4
DBP	AS	11	71±16.4	85.8±13.6	**89.9±17.9***	88.1±18.2	**91.7±16.1***	**92.4±15.7***	73.8±22.7	70.7±22.8
[mmHg]	CAD	12	69.3± 9.2	80.2±19.4	83.8±19.9	84.3±19.9	83.1±19.1	81.8±18.2	65.3±13.12	67.2±13.6
MBP	AS	11	87.3±15.2	102.0±12.6	**106.9±17.3***	104.1±17.8	**108.7±14.6***	**109.2±14.7***	91.7±21.4	88.5±21.3
[mmHg]	CAD	12	86.8±11.4	96.0±20.2	99.5±20.7	99.6±20.9	99.9±19.1	97.2±18.3	83.5±13.4	86.9±14.1
SI	AS	9	34.97±3.56	33.61±2.80	32.06±3.49	31.00±2.82	30.42±3.65	30.36±3.79	**40.38±4.54***	40.88±7.66
[ml/m²]	CAD	11	42.18±11.44	42.16±7.99	39.46±5.35	37.27±5.1	35.78±6.93	36.09±5.82	43.84±10.17	**47.23±11.53***
CI	AS	9	2.21±0.59	2.59±0.52	2.31±0.55	2.23±0.47	2.15±0.40	2.16±0.41	**2.86±0.70***	2.64±0.89
[l/min/m²]	CAD	10	2.50±0.60	3.04±0.52	2.76±0.33	2.65±0.30	2.50±0.28	2.52±0.34	**3.15±0.69***	**3.09±0.65***
TPRI	AS	9	3355.3±732.3	3289.1±688.2	3890.0±979.3	3874.0±950.9	**4265.1±1027.2***	**4237.6±997.1***	2885.2±909.7	3074.1±1046.2
[dyn*s*m²/cm⁵]	CAD	10	2785.4±653.5	2500.3±668.4	2777.1±611.6	2855.6±650.1	3155.1±830.0	3025.5±846.1	**2127.3±578.7***	2243.5±923.3

Bold and values marked with*– indicate a statistically significant difference when compared to Baseline values, $p<0.05$

4.2.1 Heart rate (HR)

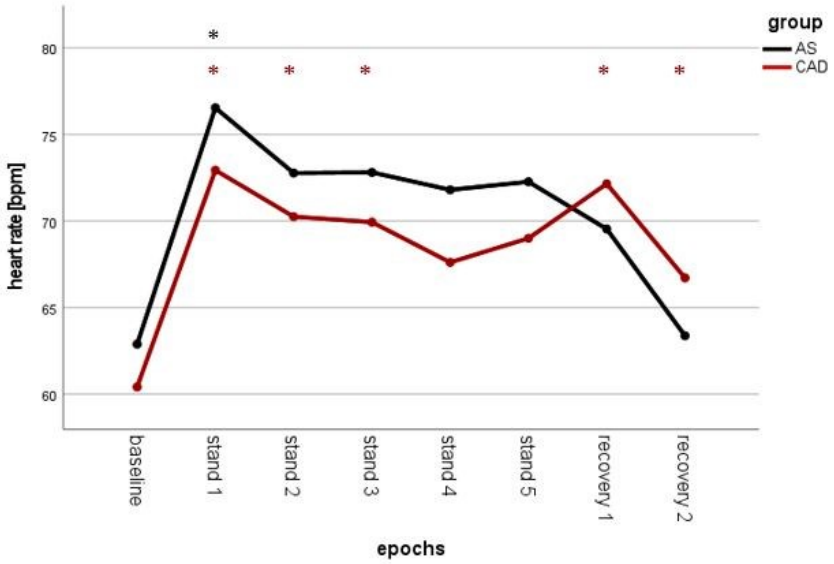


*Figure 9: HR changes over the course of the supine-to-stand test within the AS (black, n=11) and CAD (red, n=12) groups, * indicate significant changes (p<0.05) from baseline in the rmANOVA*

The results of the repeated measures ANOVA showed that the protocol exerted a significant effect on HR in both groups. The results of the mixed ANOVA indicated that no significant differences between groups existed, and no significant interaction effect of group x epochs, meaning no differences in the reactions to the supine-to-stand protocol were found between groups, see Table 5.

In the AS group, standing up induced an increase in HR, which was significant compared to Baseline at Stand 1. HR fell and stabilized after the initial peak at Stand 1 and then remained relatively constant for the remainder of the standing period. After shifting back to the supine position, HR progressively returned to near baseline values at Recovery 2, at which point the reduction in HR was significant compared to Stand 1, 2, 4 and 5.

In the CAD group, the increase in HR was similarly significant compared to Baseline at Stand 1, 2 and 3, but only reached trends at Stand 4 and 5, also seen in the slight dips at the later standing epochs. The shift back to the supine position, then caused a temporary increase in HR, that only began to decrease again at Recovery 2. Both recovery values remained significantly higher than Baseline values.

Table 7: Significant changes of HR within AS and CAD groups over the course of the protocol, assessed by pairwise comparison from the repeated measures ANOVA, M_{diff}=mean difference, Sign.=significance, 95% CI=95% confidence interval

Group	n	Epochs	M_{diff} [bpm]	Sign.	95% CI
AS	11	Baseline → Stand 1	+13.7	p=0.021	[25.7, 1.6]
		Stand 1 → Recovery 2	-13.2	p=0.001	[-21.2, -5.164]
		Stand 2 → Recovery 2	-9.4	p=0.012	[-17.1, -1,7]
		Stand 4 → Recovery 2	-8.4	p=0.033	[-16.4, -0.5]
		Stand 5 → Recovery 2	-8.9	p=0.030	[-17.1, -0.7]
CAD	11	Baseline → Stand 1	+12.5	p<0.001	[17.8, 7.3]
		Baseline → Stand 2	+9.8	p<0.001	[15.5, 4.2]
		Baseline → Stand 3	+9.5	p<0.001	[14.5, 4.5]
		Baseline → Recovery 1	+11.7	p=0.007	[20.6, 2.9]
		Baseline → Recovery 2	+6.3	p=0.014	[11.6, 1]

4.2.2 Stroke volume index (SI)

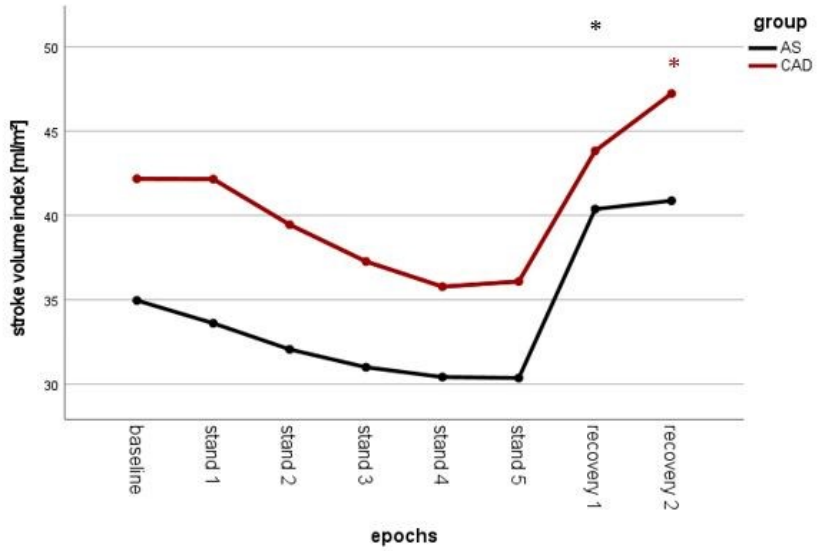


*Figure 10: SI changes over the course of the supine-to-stand test within the AS (black, n=9) and CAD (red, n=11) groups, * indicate significant changes from baseline in the rmANOVA*

The results of the repeated measures ANOVA indicated a significant effect of the protocol on SI in both groups. The results of the mixed ANOVA could not be interpreted, due to violations of the homogeneity of error variance reported above and are consequently not reported. Significant changes in the rmANOVA are reported in Table 8. In both groups, standing up elicited no significant change in SI compared to baseline. As can be seen in Fig. 10, absolute and SI values were consistently different between groups, yet the reactions to the protocol were very similar at different levels.

SI continuously declined, though not significantly compared to Baseline, mostly during the first 30 seconds of standing in both groups and reached its lowest values around the late standing epochs. Shifting back to the supine position caused an instantaneous increase in both groups.

In the AS group, the increase in SV and SI at Recovery 1 was significant compared to Baseline and Stand 3. For SI, a significant difference between Recovery 1 and stand 4 was also observed, but not for SV (see Chapter 8. Table 20).

In the CAD group, the reaction was quasi analogous, with no significant changes compared to Baseline during stand, while the shift back to supine elicited a significant increase at Recovery 2 compared to Baseline in SI.

Table 8: Significant changes ($p<0.05$) of SI within the AS and CAD groups over the course of the protocol, assessed by pairwise comparison from the repeated measures ANOVA, M_{diff}=mean difference, Sign.=significance, 95% CI=95% confidence interval

Group	n	Epochs	M_{diff} [ml/m²]	Sign.	95% CI
AS	9	Baseline → Recovery 1	+5.4	p=0.004	[9.1, 1.7]
		Stand 3 → Recovery 1	+9.4	p=0.039	[0.4, 18.4]
		Stand 4 → Recovery 1	+10	p=0.048	[0.1, 19.9]
CAD	11	Baseline → Recovery 2	+5.06	p=0.033	[0.29, 9.82]

4.2.3 Cardiac index (CI)

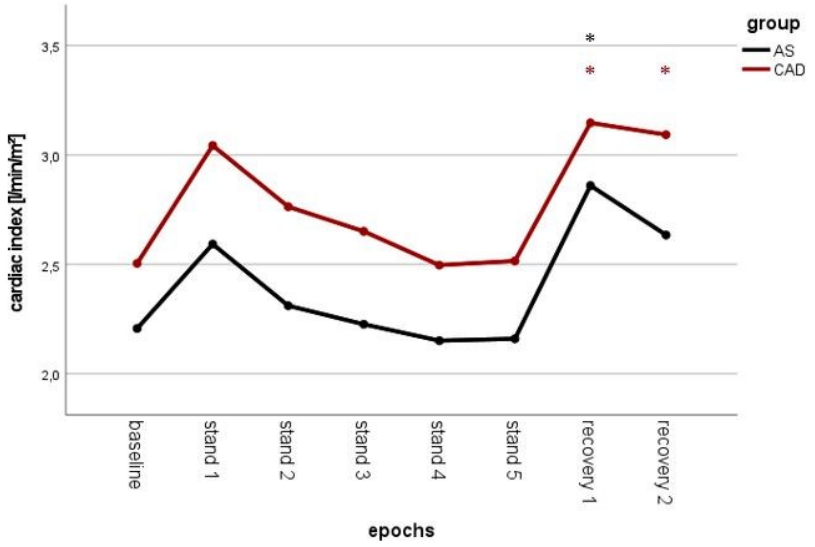


*Figure 11: CI changes over the course of the supine-to-stand test within the AS (black, n=9) and CAD (red, n=11) groups, * indicate significant changes from baseline in the rmANOVA*

The repeated measures ANVOA indicated a significant effect of the protocol on CI in both groups, while the mixed ANOVA demonstrated hinted at a trend towards significant group differences for CI, yet no interaction effect of group x epochs was seen for either parameter. The reaction to the protocol was therefore not markedly different between groups for CO and CI. Interestingly the mixed ANOVA demonstrated a significant main effect of groups for CO, but not CI (Chapter 8, Table 18). Significant changes in the rm ANOVA are presented in Table 9.

This lack of interaction is also represented in the graphs in Fig. 11, where the plotted lines run basically parallel at different levels for both groups, with the AS group showing consistently lower CI values. This is reflective of the behavior of HR and SI discussed above, from which CI is derived (see Figure 7, 9 and 10).

Generally, the shift to the standing position induced an initial increase in CI from Baseline in both groups, which failed to reach statistical significance. Since SI remained stable for both groups, and only the HR was significantly altered in both groups upon standing up, this peak must have been mediated by the initial HR increase. Consequently, as HR stabilized an SI continued to decline, so did CI, reaching Baseline levels at Stand 4 and 5. The shift to supine then induced a significant increase in CI in both groups, which was derived from the substantial increase in SI upon laying down.

In the AS group only Recovery 1 was significantly higher than Baseline values. In the CAD group, CI at Recovery 1 and 2 were significantly higher than Baseline values.

Table 9: Significant changes ($p<0.05$) of CI within the AS and CAD groups over the course of the protocol, assessed by pairwise comparison from the repeated measures ANOVA, M_{diff}=mean difference, Sign.=significance, 95% CI=95% confidence interval

Group	n	Epochs	M_{diff} [l/min/m²]	Sign.	95% CI
AS	9	Baseline → Recovery 1	+0.65	p=0.022	[0.08, 1.23]
CAD	10	Baseline → Recovery 1	+0.64	p=0.002	[0.23, 1.05]
		Baseline → Recovery 2	+0.59	p=0.026	[0.06, 1.12]

4.2.4 Total peripheral resistance index (TPRI)

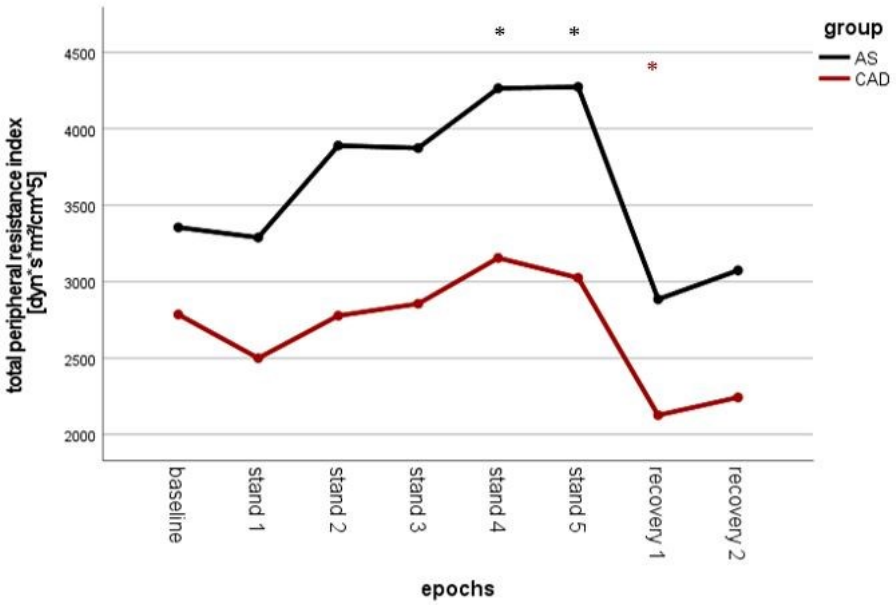


Figure 12: TPRI changes over the course of the supine-to-stand test within the AS (black, n=9) and CAD (red, n=10) groups, ** indicate significant changes from baseline in the rmANOVA*

As demonstrated in the repeated measures ANOVA, the protocol exerted significant influence on TPRI in both groups. The mixed ANOVA additionally demonstrated significant group differences in TPRI, with the AS group consistently presenting higher values of resistance. Yet, no significant interaction effect of epochs x group was observed, which suggests that the reaction to the protocol was not significantly different, when examined by the underlying cardiac condition. Significant changes within groups are elucidated in Table 10. In response to standing up, both groups showed an immediate, non-significant dip in resistance, followed by a gradual rise over the standing period.

In the AS group, the increase in TPRI reached significance compared to Baseline at Stand 4 and Stand 5. In the CAD group, the increase of TPRI during the standing period failed to reach significance at any epoch.

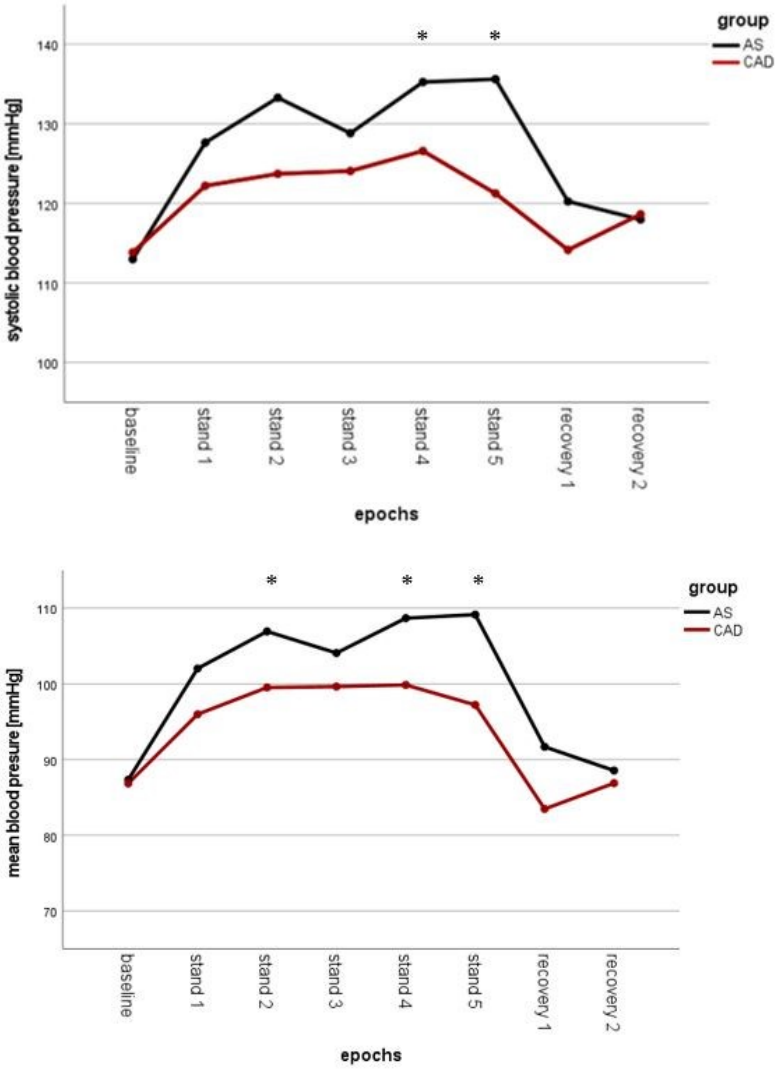
After returning to the supine position, TPRI dropped immediately upon the shift, and only recovered minimally in Recovery 2. In the AS group, TPRI at Recovery 1 was significantly lower than during Stand 2, 3, 4 and 5. While Recovery 2 was only significantly lower than Stand 5.

In the CAD group, the drop in resistance at Recovery 1 was significant for both TPR and TPRI compared to Stand 2, 3, 4 and 5 and even reached significance for TPRI when compared to Baseline values (Chapter 8, Table 22). TPR and TPRI were also still significantly lower during Recovery 2 than during Stand 4.

Table 10: Significant changes ($p<0.05$) of TPRI within the AS and CAD groups over the course of the protocol, assessed by pairwise comparison from the repeated measures ANOVA, M_{diff}=mean difference, Sign.=significance, 95% CI=95% confidence interval

Group	n	Epochs	M_{diff} [dyn*s*m²/cm⁵]	Sign.	95% CI
AS	9	Baseline → Stand 4	+910	p=0.023	[1709, 110]
		Baseline → Stand 5	+918	p=0.003	[1504, 332]
		Stand 2 → Recovery 1	-1005	p=0.009	[-1775, -235]
		Stand 3 → Recovery 1	-989	p=0.042	[-1950, -28]
		Stand 4 → Recovery 1	-1380	p=0.031	[-2658, -102]
		Stand 5 → Recovery 1	-1388	p=0.018	[-2568, -209]
		Stand 5 → Recovery 2	-1200	p=0.022	[-2253, -146]
CAD	10	Baseline → Recovery 1	-658	p=0.041	[-1296, -21]
		Stand 2 → Recovery 1	-650	p=0.020	[-1217, -83]
		Stand 3 → Recovery 1	-728	p=0.018	[-1354, -102]
		Stand 4 → Recovery 1	-1028	p=0.007	[-1797, -259]
		Stand 5 → Recovery 1	-898	p=0.017	[-1665, -132]
		Stand 4 → Recovery 2	-912	p=0.008	[-1608, -216]

4.2.5 Systolic (SBP), diastolic (DBP) and mean blood pressure (MBP)



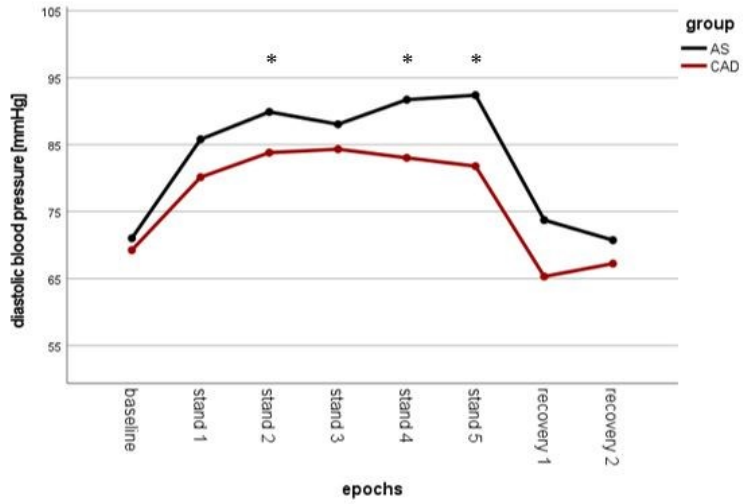


*Figure 13: SBP, DBP, MBP changes over the course of the supine-to-stand test within the AS (black, n=11) and CAD (red, n=12) groups, * indicate significant changes from baseline in the rmANOVA*

As shown in Table 4 the protocol elicited significant changes in SBP, DBP and MBP in the AS group, while in the CAD group, only the changes in DBP and MBP met significance. The mixed ANOVA showed no significant main effect of group and no significant interaction effect of epochs x group. Therefore, it can be concluded that the protocol induced significant changes in the blood pressure response in each group but caused no different reaction to the supine-to-stand test between groups.

Standing up induced an instantaneous increase in all blood pressure values across both groups, which was mostly sustained throughout the entire standing period. In the AS group, all blood pressure parameters declined temporarily at Stand 3, but rose to their respective maxima at Stand 4 and 5. In the AS group the increase in SBP reached significance compared to Baseline at Stand 4 and 5, which exceeded a mean increase of 20 mmHg from Baseline at these points of the protocol. Similarly, for DBP and MBP Stand 2, 4 and 5 were significantly higher than Baseline in the AS group.

In the CAD group, the increases in SBP, DBP and MBP were substantial but less pronounced than in the AS group and did not reach significance compared to Baseline for the entirety of the standing period. Furthermore SBP, DBP and MBP appeared to fall during the last standing epoch, whereas in the AS group, all blood pressure metrics continued to rise albeit only numerically and not significantly so.

After the return to the supine position in Recovery, blood pressure values plummeted in both groups. In both groups Recovery values were not significantly different from Baseline values. In the AS group, SBP proceeded to fall during Recovery 1 and 2, the decrement of which failed to reach significance when compared to the SBP values of standing. DBP values in the AS group, during Recovery 1 and 2, were significantly lower than Stand 4 and 5. Recovery 2 values were additionally significantly lower than Stand 2. Likewise, MBP values during Recovery 2 were significantly lower than Stand 4 and 5.

In the CAD group, the difference in SBP after shifting back to supine was again substantial but failed to reach significance compared to Baseline and standing values. For DBP Recovery 1 was significantly lower than Stand 1 to 5, while Recovery 2 still differed significantly from Stand 2 to Stand 4. The MBP values during Recovery 1 were also significantly lower than during Stand 2 to Stand 4.

Table 11: Significant changes (p<0.05) of SBP, DBP, MBP in the AS group over the course of the protocol, assessed by pairwise comparison from the repeated measures ANOVA, M_{diff}=mean difference, Sign.=significance, 95% CI=95% confidence interval

Parameter	n	Epochs	M_{diff} [mmHg]	Sign.	95% CI
SBP	11	Baseline → Stand 4	+22.3	p=0.010	[-40, -4.7]
		Baseline → Stand 5	+22.6	p=0.030	[-43.7, -1.6]
DBP	11	Baseline → Stand 2	+18.9	p=0.033	[36.6, 1.1]
		Baseline → Stand 4	+20.7	p=0.002	[34.5, 6.9]
		Baseline → Stand 5	+21.4	p=0.003	[35.8, 6.9]
		Stand 4 → Recovery 1	-18	p=0.006	[-31,5 -4.4]
		Stand 5 → Recovery 1	-18.7	p=0.023	[-35.4, -2]
		Stand 2 → Recovery 2	-19.2	p=0.034	[-37.3, -1.1]
		Stand 4 → Recovery 2	-21	p=0.002	[-34.9, -7.1]
		Stand 5 → Recovery 2	-21.7	p=0.008	[-38.4, -5]
MBP	11	Baseline → Stand 2	+19.6	p=0.040	[38.6, 0.6]
		Baseline → Stand 4	+21.4	p=0.004	[36.7, 6]
		Baseline → Stand 5	+21.8	p=0.006	[38.2, 5.5]
		Stand 4 → Recovery 1	-17	p=0.020	[-31.9, -2.2]
		Stand 4 → Recovery 2	-20.1	p=0.006	[-35.3, -5]
		Stand 5 → Recovery 2	-20.6	p=0.020	[-38.6, -2.6]

Table 12: Significant changes (p=0.05) of DBP and MBP in the CAD group over the course of the protocol, assessed by pairwise comparison from the repeated measures ANOVA, M_{diff}=mean difference, Sign.=significance, 95% CI=95% confidence interval, no significant changes in SBP were observed over the course of the protocol

Parameter	n	Epochs	M_{diff} [mmHg]	Sign.	95% CI
DBP	12	Stand 1 → Recovery 1	-14.8	p=0.024	[-28.3, -1.4]
		Stand 2 → Recovery 1	-18.5	p=0.006	[-32.5, -4.5]
		Stand 3 → Recovery 1	-19	p=0.002	[-31.3, -6.7]
		Stand 4 → Recovery 1	-17.7	p=0.006	[-31.1, -4.3]
		Stand 5 → Recovery 1	-16.5	p=0.012	[-30, -2.8]
		Stand 2 → Recovery 2	- 16.6	p=0.008	[-29.6, -3.6]
		Stand 3 → Recovery 2	-17.1	p=0.002	[-28.4, -5.8]
		Stand 4 → Recovery 2	-15.8	p=0.016	[-29.3, -2.3]
MBP	12	Stand 2 → Recovery 1	-16.1	p=0.025	[-30.6, -1.5]
		Stand 3 → Recovery 1	-16.2	p=0.009	[-29.1, -3.3]
		Stand 4 → Recovery 1	-16.4	p=0.010	[-29.6, -3.1]

4.3 Orthostatic blood pressure dysregulations within groups

After identifying the unexpected blood pressure responses to active standing in the groups above, we applied the adapted definitions laid out in Chapter 3.7 to the individual data to identify those who fulfilled our adapted criteria for overt orthostatic blood pressure dysregulations. The following analysis is provided as additional information and exploration of the hypertensive orthostatic responses. Table 16 gives an overview over how many patients in total and in each group fulfilled the definitions for OHT.

Table 13: Orthostatic hypertension (OHT) in the AS and CAD group, ASOHT and CADOHT group characteristics, mean-change(Δ) in blood pressures

	AS	**CAD**
n	11	12
Subgroup	**AS OHT**	**CAD OHT**
OHT at 3 min	7 (64%)	4 (33%)
Male	3	4
Female	4	0
Age*	74.3 ± 4.7*	66.5 ± 6.1*
Weight	80.5 ± 6.2	86.3 ± 6.1
Height	168.7 ± 10.9	174.8 ± 4.2
BMI	28.7 ± 3.6	28.3 ± 2.3
BSA	1.88 ± 0.11	2.02 ± 0.07
Blood pressure change (Δ)		
Mean Δ-SBP [mmHg]	30.0 ± 10.7	28.7 ± 7.6
Mean Δ-DBP [mmHg]	24.9 ± 10.4	28.8 ± 7.5
Mean Δ-MBP [mmHg]	27.3 ±10.3	29.5 ± 7.0

Values expressed as means ± SD
*indicate significant group differences $p<0.05$

An increase in SBP ≥20 mmHg between Baseline and Stand 4 or increase above 140/90 in subjects that were normotensive when supine, was observed in 11 (47.8%) patients across both groups. In the AS group 7 out of 11 patients or 64% (3 male, 4 female) concurred with the definition of OHT while in the CAD group 4 of 12 patients (33%) (all male) concurred with the definition. One subject in the OHT group had a BP increase to above 140/90 mmHg, from high-normal BP at Baseline, while all others displayed an in SBP increase ≥20 mmHg. Patients in the AS OHT group were significantly older than patients in the CAD OHT group.

Of the 11 patients in both groups identified with a hypertensive response, 3 subjects (27%) presented with Baseline BP measurements that would be deemed hypotensive, meaning <100 mmHg SBP.(63) During stand 7 of 11 patients displayed SBP values >140 mmHg, and 5 subjects were hypertensive as per ESC definition (>140/90 mmHg).(82) At 3 minutes of standing, 2 subjects in the CAD group fulfilled the criteria for OH laid out in Chapter 3.7 with a reduction of SBP ≥20 mmHg or DBP ≥10 mmHg, with one patient displaying sufficient reductions in both SBP and DBP (Δ-SBP= -24.6 and Δ-DBP:-14.3 mmHg), while one patient displayed a reduction of ≈10 mmHg in DBP (Δ-SBP= -13.3 and Δ-DBP=-9.987≈10.0 mmHg) at 3 minutes of standing compared to Baseline.

The patient with the more pronounced drop in both blood pressure values, showed a reduction in TPRI of 51.6% from baseline and an increase in CI by 13.6%. The subject with the modest SBP decrease and more pronounced DBP decrease displayed a stable TPRI, with an increase of only 3.2% and a CI reduction of 21.4%.

To investigate the mechanism of the hypertensive response, we isolated those with hypertensive responses at Stand 4 (3 minutes of standing) within their respective groups and classified them as AS OHT and CAD OHT. We then conducted a 2x2 mixed ANOVA, comparing the hemodynamic responses at baseline and Stand 4 for CI and TPRI between these new groups, the results of which are reported below.

Table 14: Results of the 2x2 mixed ANOVA for CI and TPRI across the ASOHT and CADOHT groups

Parameter	n total	Factor	Result
CI	10	Epochs	F(1,8)=1.827, p=0.214, η2=0.186
		Group	F(1,8)=0.890, p=0.373, η2=0.100
		Epochs x Group	F(1,8)=0.169, p=0.692, η2=0.021
TPRI	10	**Epochs***	**F(1,8)=10.675, p=0.011, η2=0.572**
		Group	F(1,8)=1.723, p=0.226, η2=0.177
		Epochs x Group	F(1,8)=0.167, p=0.693, η2=0.020

*statistical significance, p<0.05

Table 15: Means of hemodynamic parameters in the ASOHT and CADOHT groups

Parameter	Group	N	baseline	stand 4
CI	ASOHT	6	2.07 ± 0.6	2.21 ± 0.39
[L/min/m²]	CADOHT	4	2.25 ± 0.39	2.51 ± 0.29
TPRI	ASOHT	6	3327 ± 592	4055 ± 471
[dyn*s*m²/cm^5]	CADOHT	4	2905 ± 908	3471 ± 777

values expressed as means ± SD

The results of the 2x2 mixed ANOVA showed a significant main-effect of epochs, only for TPRI, while no significant main-effect for CI was observed. Furthermore, no significant interaction effects of group x epochs or main effect of group was observed. Thus, no significant group differences were observed, and group did not significantly impact changes in hemodynamic parameters over the protocol.

The only significant change was observed in resistance index values. Surprisingly, the group means for CI and TPRI in each subgroup, were similar to those of their respective superordinate group (see Table 6 and 15). While the primary reliance on TPRI stated above, seemed to hold true when interpreting the group means of AS OHT and CAD OHT, the individual changes in TRPI and CI demonstrated in Figure 14, 15 and Table 16, show that the mediation of the blood pressure increase was not uniform but heterogenous even within the hypertensive responders. Some subjects with a hypertensive response show reductions of TPRI and an increase of CI.

In the CAD OHT group, 2 subjects showed an increase in TPRI and concurrent decrease in CI, while 2 subjects displayed an opposite pattern. In the AS OHT group, all subjects showed varying degrees of TPRI increase. 2 patients showed an accompanying decrease in CI, while 4 patients showed varying degrees of CI increment. In both groups, those with the lowest CI seemed to demonstrate an increase of CI upon standing, while those with higher CI, demonstrated relative reductions upon standing (Table 16 and Figure 15).

Table 16: Individual values for CI and TPRI at Baseline and Stand 4 of subjects in the ASOHT and CADOHT groups and their relative changes in %

		CI [ml/min/m²]			**TPRI [dyn*s*m²/cm^5]**		
Group	**Subject**	**Baseline**	**Stand 4**	**Change in %**	**Baseline**	**Stand 4**	**Change in %**
AS OHT	1	3.10	2.99	-3.69	2206	3172	30.45
	2	1.71	2.02	15.44	3623	4185	13.44
	3	1.82	1.98	8.12	3516	4543	22.60
	4	1.49	2.19	32.15	3722	4018	7.37
	5	1.84	1.96	5.80	3752	4327	13.30
	6	2.46	2.12	-16.16	3142	4084	23.08
CAD OHT	1	2.62	2.41	-8.61	1717	2816	39.04
	2	2.37	2.14	-10.29	2951	4536	34.95
	3	1.70	2.72	37.21	3928	3550	-10.64
	4	2.29	2.76	16.93	3024	2981	-1.42

Mean relative increase of TPRI in the AS OHT group was 18.4% ± 8.5%, while CI increased by an average of 6.9% ± 16.5%. In the CAD OHT group, mean relative increase of TPRI was 15.5% ± 25.2%, while CI increased by an average of 8.8% ± 22.7%.

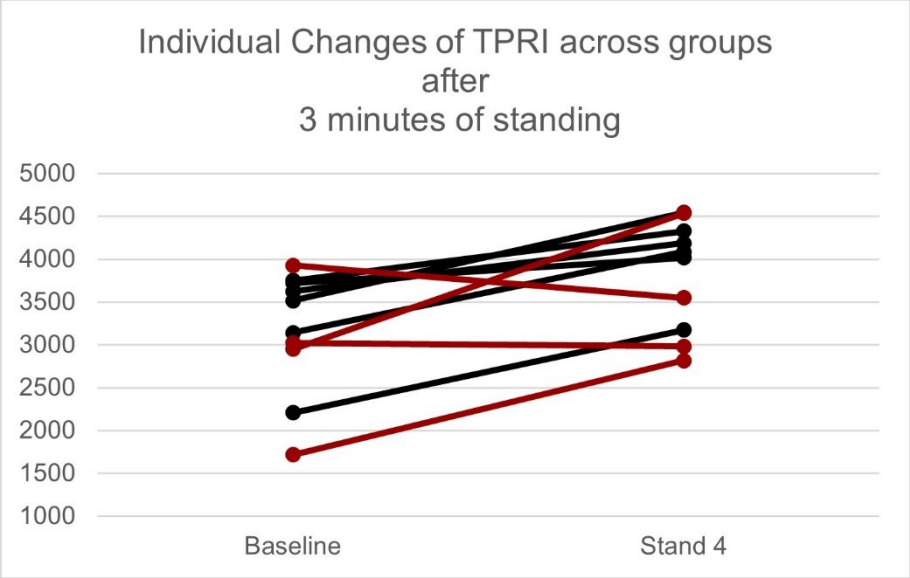


Figure 14: Individual changes of TPRI in the ASOHT (black) and CADOHT (red) groups after 3 minutes of standing compared to baseline

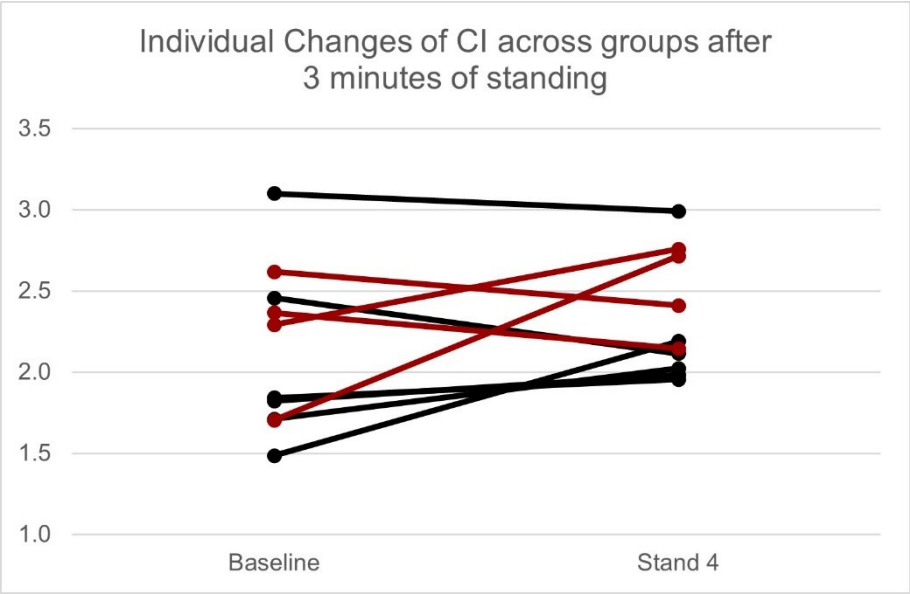


Figure 15: Individual changes of CI in the ASOHT (black) and CADOHT (red) groups after 3 minutes of standing compared to baseline

5. Discussion

5.1. CAD and Orthostasis

We hypothesized that in patients with CAD, the hemodynamic response to orthostatic stress is impaired due to alterations to the physiological mechanisms involved in countering the displacement of blood to the lower body, which were discussed in Chapter 1.4.5.

The protocol elicited significant adaptational responses to active standing in the CAD group that kept blood pressures stable in the upright posture. Standing up incurred a continuous, albeit slight and non-significant reduction in SI due to the reduction in preload. No early drop in SI was observed, which may be expected in the first 10 seconds of standing in the elderly.(11) This could have been masked the 10 second interval structure, that may average out initial SI reductions. A pronounced drop in SI and CI would be expected during the process of standing up and may therefore be hidden in the transition times, which were not included in the analysis. After the shift to the standing position the physiological HR increase temporarily increased CI, albeit not significantly. During this interval TPRI dropped numerically during the first 10 seconds of standing, corresponding to a dampened initial responses to standing.(11) The increase in HR continued to offset the incremental reduction in SI over the standing period and kept CI relatively stable at baseline levels, while TPRI rose continuously yet not significantly over the standing period. This seemed to mediate the increase in SBP, DBP and MBP, which, though not significantly higher than the Baseline level, still exceeded 10 mmHg numerically. A mean increase of >10 mmHg of SBP, DBP and MBP, and lack of CI reduction is surprising.(16) Even so, an average increase of 10 mmHg SBP upon standing does not rise to meet the current definitions of overt OHT or any other orthostatic blood pressure disturbance.

Evidence from orthostatic stress testing in patients with manifest CAD is sparse. Hori et al. (2020) showed a decrease of MBP during HUT in CAD patients before CABG, specifically at 9 and 12 minutes and a significant decrease in SV and CO by 24% at 1 and 15 minutes of tilt.(83) In our study, standing was limited to 5 minutes, thus changes from prolonged orthostasis were not to be observed. In their study SV and CO fell after tilt, while at the same time, TPR rose significantly upon tilting, thereby keeping BP relatively stable. A non-significant SV attenuation was also observed in our results, yet contrary to their findings, HR adaptation kept CO stable at Baseline levels (see Chapter 8). While passive tilting may inherently subvert the skeletal muscle pump that is working during active standing, a study comparing HUT and active standing found significant differences in the initial orthostatic

response, but no differences in hemodynamic reactions to orthostatic stress after 1 minute.(19) Cardiac autonomic dysfunction and altered baroreceptor properties in CAD have been observed.(46, 48) HR adaptation to orthostatic volume displacement and SI reductions were nonetheless able to stabilize CI in the majority of our subjects. This, in interplay with the sympathetically mediated increase in vasomotor tone, likely resulted in raised blood pressures we observed. Murata et al. (1981) investigated patients with CAD after MI and patients with congestive or hypertrophic cardiomyopathy using HUT and found diminished responsiveness of HR, TPR and CO in cardiopaths.(84) They attribute increased circulating volume in patients with impaired LV function as a possible cause of relative CO stability.(84) Lipsitz et al. (1996), in their study of drug effects on postural control in CAD patients, also found no significant reductions in CO in their baseline tilt-studies. In their study, SV declined during tilting by ~10 ml, HR increased by 10%, TPR increased by 22%, while SBP and DBP remained unchanged upon tilt.(85) In our results a numerical increase of TPRI, reduction of SI and stable CI were observed during standing that failed to reach significance compared to Baseline. Blood pressure values rose, but not significantly, over the course of standing compared to Baseline. Therefore, on average, diminished hemodynamic responsiveness in CAD patients may be somewhat confirmed by our findings.

Shifting back to the supine position incurred a significant increase in SI and CI due to the increase in ventricular preload. Initially, HR increased after shifting to supine, but normalized relatively quickly. At the same time, TPRI fell significantly. The combined effect of these hemodynamic adaptations resulted in reduced blood pressures in the supine position compared to standing. Most of these adaptations were completed and stabilized after the first 10 seconds after transition to supine, which would generally be in line with findings in healthy, younger individuals during down-tilt, though the increase in SI exceeded Baseline values. (86).

On an individual level we found strongly divergent responses to standing within the CAD group, with 2 patients showing an overtly hypotensive blood pressure response, while 4 patients displayed a hypertensive reaction to active standing. These orthostatic blood pressure dysregulations are explored in more detail in Chapter 5.4. The divergence in hemodynamic responses within the group likely contributes to the mild mean changes in the CAD group during standing, which failed to reach significance.

It can be concluded that the aggregate hemodynamic response of the CAD group to orthostatic challenges may be dampened but not gravely disturbed and the null hypothesis could therefore not be rejected. Individual data suggest that 6 out of 12 patients and thereby half of the subjects in the CAD group displayed differing orthostatic blood pressure dysregulations, which likely resulted in the general relative stability of means. Therefore, the idea of orthostatic hemodynamic stability in our CAD subjects has to be questioned and is likely not attributable to the group as a whole. Thus, in the future, distinct experimental CAD groups may need to be studied and subjects with overt disturbances isolated from the aggregate to better differentiate hemodynamic postural patterns.

5.2 AS and Orthostasis

We hypothesized that orthostatic hemodynamic regulation is impaired in patients with severe AS, due to structural and functional changes to the cardiovascular system and the autonomic cardiovascular regulation.

Standing up induced a pronounced elevation of blood pressures, which was initially mediated by a non-significant CI peak and later dominated by a progressive and significant increase in resistance. The increase in HR allowed to offset the progressive reduction in SI which in turn allowed an immediate peak of CI. These early adjustments are largely in accordance with findings in healthy elderly individuals.(87) The mean increase in blood pressures exceeded 20 mmHg across SBP, DBP and MBP at 3 and 5 minutes of standing. While mean values for SBP remained <140 mmHg, mean DBP exceeded 90 mmHg at these points of the protocol and could therefore be categorized as hypertensive according to the ESC guidelines.(82) Since the increase of SBP from Baseline during standing exceeded 20 mmHg at Stand 4 and 5 and thereby after 3 minutes of standing, we argue that on average the criteria for OHT laid out in Chapter 3.7 were fulfilled. The overall hemodynamic postural regulation was impaired, and the null hypothesis rejected. The stability of CI, which was also seen in the CAD group is remarkable, but due to the absence of healthy controls it cannot be conclusively described as abnormal. As demonstrated in chapter 4.3, 7 of the 11 subjects in the AS group or 64% fulfilled the criteria for OHT laid out above, a surprisingly high prevalence, while none developed OH. These findings are further discussed in Chapter 5.4.

Returning to the supine position increased preload, and thus SI significantly, while HR fell. Still CI rose significantly beyond Baseline levels, while resistance declined rapidly below Baseline measurements. These alterations during shifting to supine are consistent with

findings in young healthy individuals and do not appear maladaptive.(86) Pharmacological reductions of afterload have shown that cardiac output could feasibly be augmented in AS patients with low gradients by reducing filling pressures and arterial pressures but raising mean gradient.(88) This would be corroborated by our finding of increased CI in the presence of vascular afterload reductions upon recumbency.

In our AS cohort absolute SI and CI values were remarkably low. CI values in the AS group were lower than what is to be expected in healthy elderly individuals and approached values seen with varying degrees of HF.(89) Conversely TPR and TPRI were found to be relatively high in comparison to normal ranges already at Baseline to maintain normal blood pressures.(90) The lack of healthy controls, and the limitations of ICG discussed in 5.5, limit the informative value of the absolute measured values. However, the values of TPRI are also significantly higher than in the CAD subjects (see Chapter 5.3). It has been suggested, that the predominance of resistance and LV afterload in AS patients may be primarily caused by vascular load instead of overwhelming valvular resistance found in the past.(91) Laskey et al. (2009) have shown that systemic vascular resistance was markedly higher than in healthy controls at rest and during exercise in patients with AS, who undergo supine exercise testing.(92) In our group subjects were older and exhibited even higher TPR at rest (1773.9±370 vs. 1425±317 dyn*s/cm^5) at lower CO, SBP, DBP and MBP values. Hachicha et al. (2009) reported on the prognostic value of valvuloarterial impedance (Zva) - a surrogate of combined valvular and vascular LV afterload - as a predictor of poor outcomes in AS. In their study, patients with the highest Zva (≥4.5 $mmHg*ml^{-1}*m^2$) had similar baseline resistance parameters (1,824 ± 398 dyn*s/cm^5 vs. 1773.9±370.0 dyn*s/cm^5) as ours at rest. These patients also showed considerably diminished SV, SI, CO and CI (65 ± 15 ml, 35 ± 7 ml/m^2, 4.6 ± 1.1 l/min; 2.5 ± 0.5 $l/min/m^2$). These values are also in accordance with our Baseline findings (see Table 6).(93) Yotti et al. (2015) found lower TPRI values than we did, in subjects with lower Zva values (~4.1 $mmHg*ml^{-1}*m^2$) than those examined by Hachicha et al.(94) They also found an increase in arterial resistance and stiffness measures after TAVR and emphasized, that vascular and valvular load in AS are not merely complementary but also competitive, meaning mutually dependent. They urge caution in the interpretation of hemodynamic data in AS, since valvular properties likely influence the downstream vascular response.(94) Based on these characteristics, our cohort may be best identified as patients with high combined afterload (Zva), high peripheral resistance and thereby possibly high degrees of vascular load. The lack of echocardiographic data for this thesis, limits the

applicability of these findings to ours. Nonetheless, the findings discussed above corroborate that baseline resistance is likely elevated in the AS patient, and may play a chief role in the maintenance of BP. In fact, the general BP increase was primarily driven by an increase in TPRI and relatively stable CI during later standing periods in our AS subjects (see Table 6).

Literature on orthostatic stress testing in patients with AS is scant. Porta et al. (2020) conducted active stand testing and hemodynamic variability analysis in patients undergoing SAVR but did not specify the underlying valvular condition, thus the applicability of their findings to our AS group remains questionable.(95) The authors found no increase in mean SBP and MBP upon standing before surgery and only a 10 mmHg increase in DBP. They reported reduced vagal and baroreflex control in their SAVR cohort before surgery and dampened vagal withdrawal and sympathetic tone increase upon standing, leading the authors to conclude that SAVR patients suffer from impaired cardiovascular control mechanisms before surgery. Torres-Arellano et al. (2021) assessed HRV indices and their orthostatic changes in subjects with moderate to severe AS and healthy controls.(73) They also found that supine parasympathetic cardiac response was attenuated in patients with AS and accompanied by sympathetic predominance in the supine position. Since active standing led to a similar sympathetic predominance when compared to a control group, they concluded that cardiac autonomic adjustments to active standing were dampened in subjects with AS. Based on the findings of decreased transvalvular gradients and impaired cerebral perfusion during orthostasis by Dimitrow et al. (2013) and Kleczyński et al. (2016, 2020), elucidated in Chapter 1.5.5., it could be inferred that the preload dependence of the AS group would exacerbate the SV decline during preload withdrawal from standing.(67-70) This can only be partly corroborated by our findings. Mild SI decline was present, but not significant, while CI during standing was very stable compared to Baseline. Surprisingly mean BP increase and a high prevalence of OHT as opposed to OH was found. In the presence of impaired cardiovascular autonomic and specifically baroreflex function, standing blood pressure homeostasis might be impaired. Higher standing blood pressures would normally proceed to increase carotid pressure, induce wall stretch and increase baroreceptor firing, consequently reducing sympathetic nervous system activity, TPR and CO. In our study, TPRI consistently rose over the course of the protocol and CI stabilized at baseline levels, resulting in elevated blood pressures. Sympathetic baseline predominance and greater arterial stiffness could conceivably increase vascular tone and produce elevated the TPRI measures at Baseline in the

sample population of our study.(75) The increase of TPRI in our subjects may reflect even attenuated sympathetic adaptation to standing.(73)

Our findings suggest that hypertensive orthostatic responses to standing may be commonly found in patients with AS, that are characterized by increased vascular resistance and low CI. This hypertensive reaction seemed to be mediated by the aforementioned postural stability of CI and gradual increase of TPRI. Since this relationship has not been described before, more research is required to confirm our findings and further elucidate possible pathophysiological pathways.

5.3 Group differences

We hypothesized that orthostatic hemodynamic responses differ between subjects with CAD and AS since different autonomic and structural alterations of the cardiovascular and regulatory system underlie the conditions.

The general response to orthostatic stress was similar between groups since the different phases of the protocol induced comparable alterations across all hemodynamic parameters. Relative changes of HR, SI and CI were similar in magnitude between groups with slight increases in HR, slight reductions in SI and no change in CI. TPRI increase after 3 minutes was numerically stronger, in the AS group than in the CAD group. Furthermore, standing seemed to exaggerate group differences in CI and TPRI and triggered a stronger hypertensive response in the AS group since more patients in the AS group demonstrated OHT (64% vs 33%) and blood pressures during standing were at least numerically higher. While significant group differences were found in the results of the mixed ANOVA for CO, TPR and TPRI as well as a trend for CI, no significant interaction effect for epochs x group was observed for any parameter. Based on these results, the null hypothesis that hemodynamic responses to orthostatic challenge between groups are not significantly different, cannot be rejected, since group differences in hemodynamic parameters did not translate into a significant difference in reaction to orthostatic stress.

The significant difference in transition times to standing may have confounded the reported group differences. O'Connor et al. (2020) demonstrated that prolonged transition times in orthostatic challenges dampen the initial BP and the HR responses and alter the recovery response to active standing.(96) Both groups displayed median transition times that exceeded 20 seconds during standing up. The median transition time in the AS group was almost 30 seconds longer than in the CAD group, possibly further dampening the orthostatic

load imposed on the subjects and suppressing findings of initial orthostatic dysregulations. No significant drop in SI, CI or TPRI, that may be expected during the initial response, was observed in either group, which may be the result of these long transition periods. (11)

While the transition to supine induced an increase in HR in the CAD group, in the AS group HR immediately fell upon laying down. In healthy individuals, an immediate peak in HR after tilt back may be observed and may therefore be expected.(86) Even though T2 was not significantly different between groups, median transition time still differed by a total of 10 seconds. Therefore, the long transition time may have again obfuscated an initial increase in HR in the AS group. At the same time, CI increased significantly in both groups due to preload and SI upsurge. As was discussed above, the hypothesis of CO fixation in AS is progressively scrutinized. Lindman and Otto (2013) attribute more importance to vascular load in CO modification in AS, in their editorial of Eleid et al..(91) The latter demonstrated, that vasodilation with nitroprusside reduced TPRI and improved CI without HR alteration and also showed a trend towards the improvement of SI, in patients with low gradient AS.(88) The reduction of the vascular afterload component in the AS group may therefore have made the CI increment feasible, similar to the CAD group.

The severely skewed sex distribution between groups - the CAD group is entirely comprised of men, while the AS group comprises men and women - may have heavily influence the described differences between groups in CO, CI, TPR and TPRI. This may contribute to the group differences in CO and TPR found but should be attenuated to some degree due to the advanced age and indexation for BSA. Even though no significant differences in biometric data were found between groups, height, weight and BSA were still numerically higher in the CAD group, likely due to said difference in sex distribution. Consequently, we saw an attenuation of group differences for CI as the mixed ANOVA showed significance for the group difference in CO only, and only a trend for CI (see Chapter 4.2.3). Yet little to no attenuation of the significant difference between groups in vascular resistance was observed when indexation for BSA was considered. Studies have found conflicting evidence regarding the influence of biological sex on orthostatic tolerance. Some suggested that in persons <45 years of age, orthostatic tolerance may be more dependent on vascular resistance in men than in women.(97, 98) One study in elderly subjects found, that women had stronger increases in TPR in response to standing than did elderly men.(99) Yet, tilting studies have shown stronger decrements of systolic blood pressure, weaker sympathetic blood pressure modulation and attenuated increases in plasma NE in elderly women compared to men.(100) A more

recent study found no significant differences in cardiovascular parameters in young, healthy subjects across gender in response to varying orthostatic challenges.(101) In light of conflicting results it can only be proposed that biological sex may affect the observed group differences in our results and the proposed relationship between the AS group and higher TPRI.

Absolute CI values were low in both groups. Though the ICG determination of SV may be severely limited (see Chapter 5.5), CI values <2.5 ml/min/m² would be considered abnormally low and predictive of adverse outcomes in patients with congestive HF.(102) Seoudy et al. (2021) demonstrated that subclinical congestion in patients with severe AS was present in ~62% of a sample of patients undergoing TAVR.(103) They suggest that in severe AS higher rates of underrecognized hypervolemia may be present than even in patients with congestive heart failure. Volume overload may ameliorate SV and CO drops upon standing as was suggested in early studies, that demonstrated increase postural hemodynamic tolerance in patients with HF.(104) Bronzwaer et al. (2017) studied reactions to orthostatic stress in HF patients with reduced EF and modern pharmacological management based on neurohumoral blockade. They have challenged former findings and have shown an increased rate of postural hypotension of up to 50% in patients with HF, mediated by impaired HR and TPR responses.(105). In their study, HF patients with higher NYHA class and cardiac dysfunction had attenuated SV decline and reductions in TPR upon standing. While these newer findings suggest higher incidence of OH in patients currently treated for HF, it may reinforce the relationship between cardiac dysfunction and relative stability of SV as well as attenuated autonomic adjustments upon postural shifts, that was also reported by Murata et al.(84) Unfortunately, no information on the presence of HF or the LVEF was available for the analysis in this thesis. Nonetheless, the non-significant changes in SI and CI observed during standing in our AS and CAD group may be indicative of broader cardiac dysfunction that may be present in both groups. Contrary to the findings in severe HF, TPRI increased significantly in the AS group, who on average had lower CI. Since SI reductions upon standing were of little magnitude, but numerically still preserved, this may be indicative of the fact that no severe clinical HF was present in the sample. This may be, because SAVR ought to be performed at the onset of symptoms or before, when at high risk, and prevent further deterioration of LV function.(62)

Additionally, AS and CAD often coincide in the same individuals with a prevalence of CAD of up to 50% in patients with AS. In our sample only 1 patient required additional CABG

during SAVR. Nonetheless subclinical CAD may already be present, as the prevalence of CAD in elderly patients undergoing TAVR increases to up to 65%.(106) Both groups routinely display impaired baroreflex sensitivity and general vascular stiffening, which possibly contribute to the development of OHT. Both conditions also share pathogenetic pathways that include atherosclerotic, inflammatory endothelial damage to arterial walls and valves.(107) For aortic valve sclerosis - precursor to manifest AS - strong relationships to CAD, MI and inflammation have also been established. (108) Echeverría et al. (2019) also demonstrated inflammation, impaired parasympathetic cardiac autonomic modulation and reduced autonomic adjustments to standing in patients with aortic valve sclerosis.(109) It is therefore reasonable to assume that cardiac dysfunction, atherosclerotic disease and common risk factors such as inflammation, hypertension and reduced autonomic adjustments may predispose both groups to similar blood pressure disturbances. Both groups displayed stable CI, similar HR increases and similar SI changes. The stability of circulatory parameters in both groups should be interpreted with caution for lack of a healthy control group in our experiments.

In contrast to our hypothesis, an overall similar hemodynamic reaction to orthostatic stress, was seen to differing degrees in both groups. This may also be representative of pathophysiological commonalities and similar degrees of cardiac dysfunction in these cardiovascular diseases. The lack of difference in reaction to orthostatic stress was likely due to similarly altered hemodynamic responses to standing which may be caused by the high prevalence of OHT in both samples and general orthostatic BP increase seen across most subjects in both groups. Due to the observational design, confounding and other limitations laid out in Chapter 5.5, the observed differences and commonalities between the groups cannot, with certainty, be attributed to the isolated cardiac pathologies alone.

5.4 Orthostatic blood pressure dysregulations

Upon individualized inspection of the data, we observed a surprisingly high prevalence of manifest orthostatic blood pressure dysregulations in both the AS and CAD group.

In the CAD group, 6 subjects (50%) displayed manifest disturbances, with 2 subjects (17%) showing OH and 4 displaying OHT (33%). In the AS group 7 of 11 subjects (64%) presented with OHT and none with OH.

OH has been strongly associated with the future development of CAD, HF, stroke and overall mortality.(51) It may precede the development of clinical coronary atherosclerosis as a

surrogate of atherosclerotic disease, which may lead to baroreflex loss, impaired vascular reactivity and higher degrees of blood pressure variability.(45)

It is thus reasonable to assume, that OH and autonomic dysfunction resulting from subclinical atherosclerosis persists in patients with manifest atherosclerotic disease. In fact Radaelli et al. (2014) observed that HR and BP variability as well as baroreflex function were impaired in patients with stable CAD, and no prior MI, to the extent seen in patients with chronic HF.(48) OH is most commonly caused by autonomic dysfunction and mediated by disturbances of the efferent baroreflex pathway, which leads to inadequate vascular resistance adjustments.(22) In the 2 subjects, who met the threshold for OH, statistical analysis was not conducted due the small sample size. The individual data suggests that the mechanisms were not entirely consistent, as one subject showed loss of resistance and stable CI, while the other subject displayed grave reductions of CI and an inadequate increase of vascular resistance. Nonetheless, the commonality was an inadequate resistance response upon standing, which is in accordance with the classical understanding of OH. Our findings underpin that hypotensive blood pressure disturbances may be prevalent in patients with manifest CAD, and that it may present as a surrogate of the underlying atherosclerotic disease.

Jordan et al. (2020) reviewed studies on OHT and suggested multiple pathophysiological pathways.(28) Among these, an excessive drop in preload upon standing and consequent reduction in CO, excessive venous pooling, orthostatic sympathetic hyper-excitation, increased orthostatic NE release and higher vascular NE sensitivity as well as increased vascular stiffness in the elderly were proposed as interlocking mechanisms. Magkas et al. (2019) additionally reported in their review, that higher baseline sympathetic tone and impaired baroreflex sensitivity may play a role in the inability to adjust BP to normal values.(110)

Associations of CAD with OHT are controversial. While an association of SBP increase upon standing and elevated cardiac troponin levels was observed previously, OHT has more recently only been associated with manifest PAD and stroke but not coronary disease.(34, 35) Chaves et al (2022) very recently showed a prevalence of 20% of OHT, which was thought to be surprisingly high, in elderly patients with different heart diseases. 40-50% of subjects in this study also had CAD and 90% had arterial hypertension.(111) Pathophysiological links between OHT, CAD and disease progression are lacking. Hypertension undoubtedly plays a role in the development of CAD, and is strongly associated with OHT, as is ageing.(42, 110) As vascular stiffness is implicated in the presence of OHT in the elderly

and arterial stiffness indices are commonly elevated in patients with stable CAD, vascular stiffness may play a role in the presence of OHT in our sample.(28, 112) Sympathetic overshoot upon standing or baseline appears to be a primary mechanism, driving OHT. While sympathetic overactivation at rest has been demonstrated in patients with hypertension and after myocardial infarction, such evidence is lacking for stable CAD without MI.(113) Our findings suggest that in patients with manifest CAD, different orthostatic blood pressure disturbances may emerge. Structural atherosclerotic changes and concomitant hypertension may predispose to a hypertensive reaction to orthostatic stress. As was laid out in Chapter 4.3, due to the small number of patients with OHT in the CAD group and the opposing mediation of the hypertensive response in the 4 CAD OHT patients, no uniform mechanism was identified. Two subjects showed an increase in CI, with a reduction of resistance, while 2 other patients in the groups, showed an increase in resistance and diminishing CI in response to standing. While an increase in TPR upon standing is believed to mediate OHT, a cardiac mediation is not commonly described and is therefore surprising to find.(31)

AS and OHT have not been linked in any capacity up to this point. Pathophysiological links can only be inferred but have not yet been described in the literature. OHT is commonly associated with hypertension, which is also strongly connected to the presence of AS and is believed to aggravate disease progression.(114) Kario et al. found associations of OHT with ECG surrogates of LVH and biomarkers of cardiac overload.(33) LVH is inherent to AS disease progression (see Chapter 1.5.3). Increased levels of cardiac overload biomarkers like BNP are common in patients with AS, regardless of ventricular function and are of prognostic importance.(115) While in AS, these changes result from the presence of the stenosis and consequent cardiac overload these associations may inversely be caused by BP variability and hypertension in OHT. Impaired baroreflex function was also described in patients with severe AS.(75) Several arterial stiffness indices are commonly altered in AS and may even increase after SAVR, suggesting masking of concomitant vascular dysfunction and atherosclerotic disease that contributes to the combined LV afterload.(116) Both factors may connect AS to OHT as they do in CAD. Furthermore, higher baseline sympathetic activity measured by MSNA and attenuated spontaneous baroreflex gain in AS patients have been demonstrated, which were somewhat ameliorated by TAVR.(75) MSNA is related to high TPR and low CO in young men, but less so in the elderly population in whom it correlates better with MBP only.(117, 118) The relationship between increased MSNA in AS and increased TPRI at baseline and during stand is therefore not wholly explanatory of our findings, but may

point to some degree of biological plausibility. Torres-Arellano et al. demonstrated disturbed cardiac sympathovagale balance, with lower baseline parasympathetic cardio-autonomic adjustment and attenuated sympathetic responses during standing.(73) In the hypertensive responders in the AS group, mean CI was kept relatively stable at baseline levels during standing. Yet in the individual data in Chapter 4.3, AS patients with OHT reacted by either CI reduction, stabilization or even increment from baseline to 3 minutes of standing. Resistance in hypertensive responders increased across all subjects but to a lesser degree (18.4% ± 8.5%) than the physiologically common 30-40% .(16) Higher baseline TPR may be corroborated by higher sympathetic tone at rest and higher vascular stiffness and may therefore show a dampened increase in light of attenuated sympathetic adjustments. While OHT may be characterized by sympathetic overactivation and increased NE release upon standing and not at baseline, our AS subjects seem to be more so characterized by high baseline levels of sympathetic tone and attenuated adaptation upon standing, which was analogously suggested by Bronzwaer et al. for patents with HF and OH.(105) In the presence of no CI decline from Baseline during standing, the attenuated but intact increase of resistance as an expression of lower sympathetic adaptational reserve may be sufficient to facilitate the blood pressure increase seen in our sample.

In conclusion, pathophysiological commonalities between OHT, AS and CAD and may exist. Chaves et al. demonstrated relatively high rates of OHT in cardiopaths with and without CAD and hypertension. There may be a connection between cardiac and cardiovascular pathologies and OHT in general. Higher sympathetic tone and combined valvular and vascular load as well as subclinical hypervolemia may be more present in patients with severe AS than in stable CAD and may strengthen that connection. While an increase of resistance in the OHT subgroups was predominant, the individual data suggested that cardiac as well as vascular reactive mechanisms for increasing blood pressure were present in both subgroups. CI increase was stronger in those with low Baseline CI. Murata et al. hypothesized that, analogous to nitrate application, postural reductions in preload may augment CI in patients with very low CI.(84) The heterogenous response in hemodynamic parameters among both groups points to the aforementioned difference in mechanisms, that may underlie the hypertensive response. Even with these commonalities and differences explored, no uniform mechanism or wholly plausible relationship between these conditions can be identified in this thesis or from the literature. In light of these inconclusive finding more research is required to confirm our findings and identify possible pathophysiological mechanisms.

5.5 Limitations

This thesis has several limitations that restrict the interpretation of the data and thus its informative value. Chiefly, we investigated subgroups of a randomized controlled trial, that were not aims of equalization and group homogeneity in the superordinate study. Therefore, the groups specified in this thesis were not balanced for known or unknown traits. This limitation is aggravated by the fact that no healthy controls were enrolled in the study. This resulted from the fact that comparison to healthy subjects was not the aim of the CardioVib trial. This further limit the attributability of our findings and potential group differences to the represented cardiac pathologies. Furthermore, CardioVib is a pilot-study which among other aims, was designed to assess necessary group sizes for further trials and is therefore inherently not powered to investigate group differences by observational design alone.

Apparent differences between groups are shown in Table 2. The CAD group only comprises men whereas the AS group incorporates 6 men and 5 women. Biological sex may have implications for orthostatic hemodynamic control. This has been discussed in more detail in Chapter 5.3. The numerical differences in the biometric data, meaning higher age and lower height and BSA in the AS group, did not reach significance. The non-significant group difference for CI, compared to CO still suggests that a correction for body composition by BSA in the indexed values nonetheless ameliorates some group differences of importance.

Transition times from the supine to the standing position were relatively long and markedly different between groups. The AS group took longer to transition to the standing position. The longer transitioning time could be caused by higher degrees of frailty in the AS group and may therefore be adaptational in nature. Yet, as was laid out in Chapter 1.4 and 1.5, SAVR and CABG are reserved for patients with low or intermediate surgical risk, which are suitable for extensive, high-risk surgeries as opposed to TAVR and PCI. Thus, frailty in our patient populations could arguably be relatively low as per the selection bias introduced by the chosen intervention. Regardless of the cause, long transition times of >10 seconds may obfuscate and ameliorate the initial hemodynamic adjustments to standing that were included in the analysis.(96) This is corroborated by the fact that no initial BP or SI drop was observed, as would be expected in healthy subjects and possibly even in patients with varying degrees of cardio autonomic and vascular disease.(11)

Aside from known differences, several possible confounders especially regarding the medical history are not known. Chiefly neither the degree of the coronary vessel disease, additional vascular disease or valvular pathologies, nor the AS entity (e.g., low flow low gradient, normal flow normal gradient, etc.) were known. Furthermore, relevant comorbidities, such as a possible degree of heart failure and contractile dysfunction, neurological diseases that cause autonomic dysfunction or diabetes mellitus that may result in additional autonomic neuropathy, are not reported. Specifically HF is associated with increased vascular resistance,(119) and may confound these findings across both groups as was also explored in Chapter 5.3. Medication can influence the reaction to orthostatic stress. Specifically, medication affecting the cardiovascular system is prone to disturb hemodynamic orthostatic tolerance and is naturally prescribed in patients with manifest cardiovascular disease, such as our samples.(85, 120, 121) As medication of the patients was not known, the preoperative medication management may confound our findings.

Measurements were conducted on the ward, or the ICU and patients were therefore not entirely deprived of possibly stressful stimuli. Since the measurements took place hours or days before surgery, and anxiety as well as stress levels are heightened in a majority of cardiac surgery patients, the timing of the preoperative measurement may exacerbate sympathetic responses.(122) The epochal structure using 10 second means, while better at representing short term alterations, inherently ignores longer periods of the later standing period. Therefore, no information can be provided on alterations between the epochs, and sustained alterations, required by some definitions for OH/OHT, cannot be proven definitively and their prevalence may therefore be overestimated. In fact, one subject in the OH and one in the OHT group only narrowly fulfilled very specific conditions of the definitions (see Chapter 4.3). As described in Chapter 3.7 some patients could not be included in this analysis, as the data obtained was either incomplete or of low quality and had to be excluded accordingly. In addition, means substitution for one patient had to be applied for one epoch during standing.

Lastly the measurements obtained from the TFM are susceptible to errors. In finger plethysmographs absolute values, especially so SBP values, are less reliable even though alterations in BP within subjects are well validated.(123) In contrast to many other finger plethysmograph devices, the TFM BP data are calibrated with additional oscillatory BP measurements on the other arm, which reduces error margins for BP measurements.(80). Estañol et al. (2016) demonstrated that myogenic vasoconstriction in the limbs in response to alterations

of limb position in relation to the heart level can heavily impact continuous blood pressure measurements independent of baroreflex mediated vasoconstriction.(124) Finger plethysmograph devices therefore need to be held exactly at heart level. Deviations from the heart level, may heavily alter measurements due to different hydrostatic loading and myogenic vascular response.(123) Positional disruptions may be aggravated during posture shifts and may falsify blood pressure differences between supine and standing if the position of the cuff relative to the heart level changes during transition. Thus, a systematic error with the device or its handling could cause spurious findings of increasing blood pressure. The similar magnitude of SBP and DBP increase across all groups may be indicative of a systemic error, as other studies of OHT have shown more pronounced SBP than DBP increases.(33, 34, 37)

Since CO, TPR and their indices are calculated from other parameters (see Figure 7), measurement errors in their constituent parameters would automatically be relayed to the calculated values. The TFM manual states that the impedance measurement may be unreliable in the presence of AS or aortic regurgitation.(81) The SV calculation and the values derived from SV (SI, CO, CI, TPR, TPRI) would also be spurious in the case of an erroneous measurement. Depending on how many measured values contributed to the calculation of each parameter errors in multiple measurements would enforce one another. As shown in Figure 7, TPR and TPRI may therefore be the most susceptible parameters to error as ECG, ICG and BP measurements are funneled into these parameters. TPRI may be additionally compromised, since CVP is fixed at 3 mmHg by the software. In the supine position CVP could naturally be higher especially in subjects with severe heart disease. Fixed CVP at 3 mmHg may underestimate the pressure differential between arterial and venous system, thus overestimating TPRI with the given formula.

5.6 Conclusions

Both groups displayed postural hemodynamic adaptations when exposed to orthostatic challenge by standing and reacted accordingly with an increase in HR as well as an increase in TPRI, to offset the progressive reduction of SI and were thus able to maintain CI and blood pressures. The AS group showed a significant increase in BP while maintaining relatively stable but low SI and CI as well as high TPRI. Return to the supine position improved SI, CI and lowered TPRI and BP accordingly in both groups. The aggregate increase in BP in the AS group qualifies for OHT. Thus, it can be concluded that in the AS group the hemodynamic response to orthostatic stress was impaired. 7 of 11 patients in the AS group qualified for OHT. The aggregate of the CAD group displayed no significant orthostatic hemodynamic disturbance. This is likely due to the presence of contrasting blood pressure disturbances in the CAD group. 2 patients in the CAD group suffered OH, while 4 patients qualified for OHT. No significant difference in hemodynamic responses to orthostatic stress were observed between groups. CO, TPR and TPRI differed significantly between groups. These differences did not amount to significant group differences in the reaction to the protocol, possibly due to inadequate statistical power. Therefore, no group differences in reaction to orthostatic stress were observed.

The analysis of hypertensive responders across both groups points to the increase in resistance, in the presence of relative stability of CI, as being causal in the mediation of the hypertensive response. Yet individual data showed both vascular and cardiac reactive type responses, suggesting heterogeneous mechanisms in our sample.

Due to the severe limitations and observational design of this thesis, these findings are inherently not attributable to the underlying cardiac conditions and require confirmation, more research, as well as pathophysiological exploration.

5.7 Perspectives

The possible presence of blood pressure dysregulations in patients with severe cardiac pathologies could encourage future research in these patient groups. Further research may be conducted into the presence of OH and OHT in cardiac conditions, their possible pathophysiological relationships, as well as any potential connection to clinical outcomes, since both dysregulations may be of prognostic relevance in the elderly.

6. References

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7. Supplement
Results and statistical analysis

Table 17: Results of the rm ANOVA for no-indexed values in the AS and CAD group

Group	Parameter	n	Result – repeated measures ANOVA (8 epochs)
AS	**SV***	9	F(1.732, 17.345)=9.836, p=0.003, η2=0.551
	CO*	9	F(2.302, 18.418)=6.351, p=0.006, η2=0.443
	TPR**	9	F(2.398,19.181)14.781, p<0.001, η2=0.649
CAD	**SV***	11	F(1.893, 18.927)=5.656, p=0.013, η2=0.361
	CO*	10	F(2.711,24.395)=6.016, p=0.004, η2=0.401
	TPR**	10	F(2.923,26.309)=7.859, p<0.001, η2=0.466

*statistically significant p<0.05

Table 18: Results of the mixed ANOVA – 8 epochs, 2 groups for CO and TPR

Parameter	n total	Factor	Result – mixed ANOVA
CO	19	**Epochs****	F(2.757,46.862)=11.928, p<0.001, η2=0.412
		Group*	F(1,17)=6.959, p=0.017, η2=0.290
		Epochs x Group	F(2.757,46.862)=0.222, p=0.866, η2=0.013
TPR	19	**Epochs****	F(3.468,58.950)=21.733, p<0.001, η2=0.562
		Group*	F(1,17)=11.296, p=0.004, η2=0.399
		Epochs x Group	F(3.468,58.950)=1.615, p=0.189, η2=0.087

*statistically significant p<0.05
**highly statistically significant p<0.001

Table 19: SV, CO, TPR means in the AS and CAD groups

			Means of hemodynamic parameters							
			Baseline	**Stand**					**Recovery**	
Parameter	**Group**	**N**	**Epoch 1**	**Epoch 2**	**Epoch 3**	**Epoch 4**	**Epoch 5**	**Epoch 6**	**Epoch 7**	**Epoch 8**
SV	AS	9	65.99±7.47	63.53±7.42	60.52±7.66	58.35±4.08	57.21±5.46	57.16±6.34	**76.15±8.84***	76.92±13.66
[ml]	CAD	11	82.74±21.16	81.39±13.11	77.23±7.99	73.05±7.57	70.11±12.77	71.01±11.94	85.66±16.74	**92.78±22.47***
CO	AS	9	4.15±1.03	4.89±1.01	4.36±1.08	4.19±0.83	4.05±0.67	4.07±0.74	**5.38±1.23***	4.95±1.59
[l/min]	CAD	10	4.85±1.05	5.88±0.81	5.36±0.53	5.15±0.56	4.84±0.50	4.87±0.56	**6.07±1.06***	**5.99±1.13***
TPR	AS	9	1773.9±370.0	1746.9±393.8	2057.6±509.4	2040.0±450.4	**2248.9±476.9***	**2255.3±481.9***	1521.6±466.5	1623.1±551.1
[dyn*s/cm^5]	CAD	10	1435.3±334.2	1279.1±321.6	1422.1±283.3	1464.5±316.9	1617.1±411.8	1542.6±382.3	1086.1±263.6	1151.5±297.4

Means of non-indexed hemodynamic parameters

Stroke volume (SV)

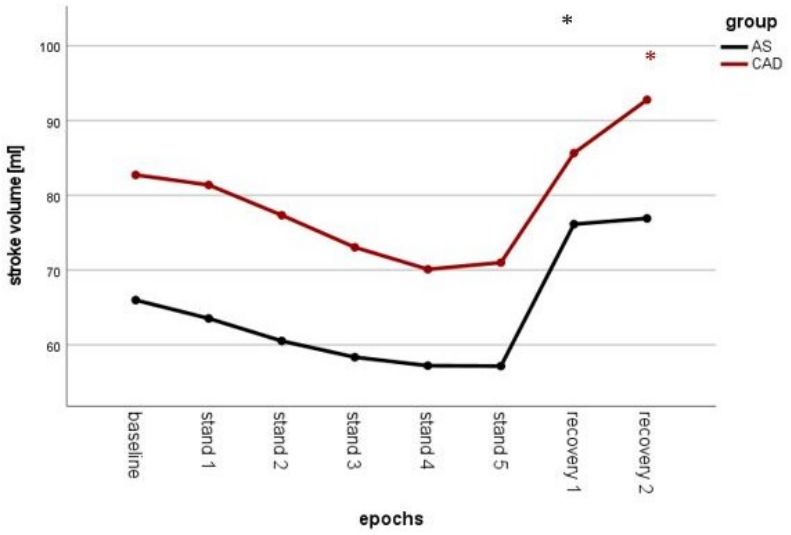

Figure 16: SV changes over the course of the supine-to-stand test within the AS (black, n=9) and CAD (red, n=11) groups,
** indicate significant changes from baseline in the rmANOVA*

Table 20: Significant changes (p<0.05) of SV within the AS and CAD groups over the course of the protocol, assessed by pairwise comparison from the repeated measures ANOVA, M_{diff}=mean difference, Sign.=significance, 95% CI=95% confidence interval

Group	n	Epochs	M_{diff} [ml]	Sign.	95% CI
AS	9	Baseline → Recovery 1	+10.2	p=0.003	[3.4, 7.1]
		Stand 3 → Recovery 1	+17.8	p=0.045	[0.3, 35.3]
CAD	11	Baseline → Recovery 2	+10.1	p=0.039	[0.38, 19.71]

Cardiac output (CO)

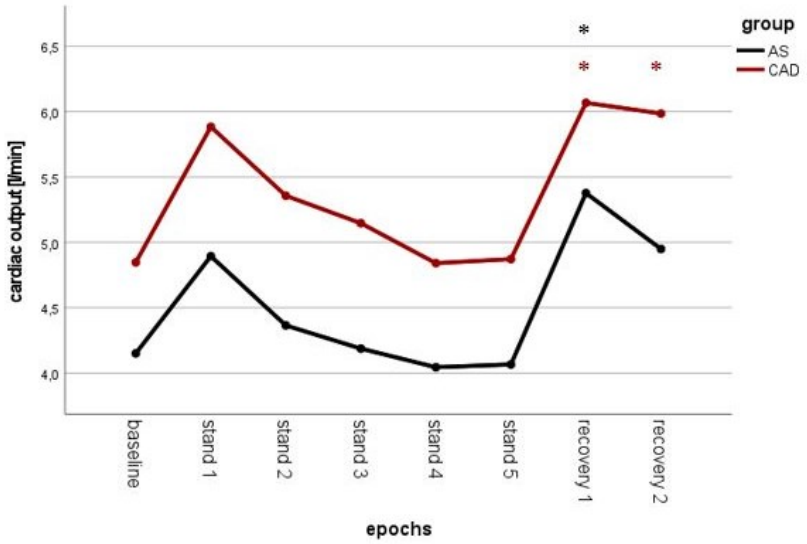

Figure 17: CO changes over the course of the supine-to-stand test within the AS (black, n=9) and CAD (red, n=10) groups,
** indicate significant changes from baseline in the rmANOVA*

Table 21: Significant changes (p<0.05) of CO within the AS and CAD groups over the course of the protocol, assessed by pairwise comparison from the repeated measures ANOVA, M_{diff}=mean difference, Sign.=significance, 95% CI=95% confidence interval

Group	n	Epochs	M_{diff} [l/min]	Sign.	95% CI
AS	9	Baseline → Recovery 1	+1.23	p=0.022	[0.16, 2.3]
CAD	10	Baseline → Recovery 1	+1.22	p<0.001	[0.52, 1.92]
		Baseline → Recovery 1	+1.14	p=0.026	[0.11, 2.17]

Total peripheral resistance (TPR)

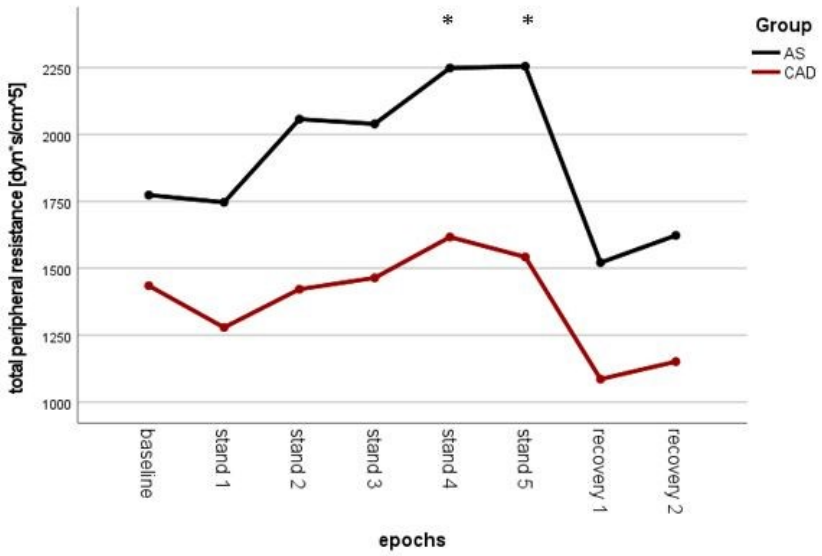

Figure 18: TPR changes over the course of the supine-to-stand test within the AS (black, n=9) and CAD (red, n=10) groups,
** indicate significant changes from baseline in the rmANOVA*

Table 22: Significant changes (p<0.05) of TPR within the AS and CAD groups over the course of the protocol, assessed by pairwise comparison from the repeated measures ANOVA, M_{diff}=mean difference, Sign.=significance, 95% CI=95% confidence interval

Group	n	Epochs	M_{diff} [dyn*s/cm^5]	Sign.	95% CI
AS	9	Baseline → Stand 4	+475	p=0.014	[862, 88]
		Baseline → Stand 5	+481	p=0.002	[769, 194]
		Stand 2 → Recovery 1	-536	p=0.009	[-948, -123]
		Stand 3 → Recovery 1	-518	p=0.038	[-1015, -22]
		Stand 4 → Recovery 1	-727	p=0.027	[-1385, -69]
		Stand 5 → Recovery 1	-734	p=0.017	[-1352, -116]
		Stand 5 → Recovery 2	-632	p=0.021	[-1184, -81]
CAD	10	Stand 2 → Recovery 1	-336	p=0.022	[-634, -39
		Stand 3 → Recovery 1	-378	p=0.024	[-716, -41]
		Stand 4 → Recovery 1	-531	p=0.009	[-943, -119]
		Stand 5 → Recovery 1	-457	p=0.015	[-836, -77]
		Stand 4 → Recovery 2	-466	p=0.009	[-830, -102]