Diplomarbeit

Effects of submaximal exercise on cardiovascular parameters during recovery from minimal invasive aortic valve replacement interventions

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Graz, den 09.07.2018

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Zusammenfassung

Einleitung: Aortenstenose ist eine der häufigsten chronisch-progressiven Klappenerkrankung der westlichen Bevölkerung. Unbehandelt führt sie zu Linksherzinsuffizienz, plötzlichem Herzstillstand, Synkopen und letztendlich vorzeitigem Tod. Daher benötigen diese PatientInnen früher oder später einen Aortenklappen Ersatz. Neue Techniken, wie die minimale Sternotomie, wurden in den letzten Jahren eingeführt und zeigten eine Überlegenheit gegenüber herkömmlichen Methoden. In der Regel werden nur harte Endpunkte wie Morbidität und Mortalität berücksichtigt, wenn das Outcome nach diesen Eingriffen beurteilt wird. Funktionelle Parameter des kardiovaskulären und autonomen Systems könnten jedoch nützliche Erkenntnisse darüber liefern, wie sich die Genesung bei diesen Patienten manifestiert. Bisher wurden kardiopulmonale Belastungstests in frühen Stadien der Genesung nicht durchgeführt. In der Literatur gibt es daher keine Erkenntnisse darüber, wie sich kardiopulmonale und autonome Parameter unter Belastungstests bei Patienten nach der Erholung von minimalen Aortenklappen Ersatz Interventionen verhalten.

Ziele & Aufgaben: Diese Studie untersuchte frühe Veränderungen in kardiovaskulärer und autonomer Funktion nach Aortenklappen Ersatz Operation, mittels submaximaler kardiopulmonaler Belastungstests. Das Ziel ist es neue Erkenntnisse über die Regeneration nach diesen minimal-invasiven Operationen zu gewinnen.

Methoden: Eine Stichprobe von 10 Aortenstenose PatientInnen wurde mit einer gesunden Kontrollgruppe (n= 10) verglichen und deren CVS und autonome Funktion mit submaximalem CPET zu drei Messzeitpunkten (präoperativ, 5 Tage postoperativ, 3 Wochen postoperativ) erhoben. Die evaluierten CVS-Parameter: Rest-HR, Peak-HR, HR-Recovery und Decrement wurden zwischen diesen drei Messzeitpunkten mittels multivariater Varianzanalyse berechnet. Die präoperativen Parameter der Aortenstenose Gruppe wurden mit der gesunden Kontrollgruppe verglichen. Da postoperativ die Hälfte der Aortenstenose PatientInnen (n=5) eine β-Blocker-Therapie mit Bisoprolol erhielten, wurde die Aortenstenose Gruppe in zwei Subpopulationen aufgeteilt, welche separat analysiert wurden.

Ergebnisse: Der erwartete Unterschied in CVS-Parametern zwischen Aortenstenose PatientInnen und gesunder Kontrollgruppe war nicht signifikant. Des Weiteren ergab sich kein signifikanter Unterschied für die Parameter Rest-HR, Peak-HR, HR-Recovery und Decrement zwischen den Zeitpunkten präoperativ und postoperativ 5 Tage. 3 Wochen postoperativ zeigte sich ein signifikant niedrigerer Peak HR (p=.002) sowie rest-HR (p=.025), sowohl in der β-blockierten als auch nicht β-blockierten Aortenstenose Gruppe. Kein signifikanter Unterschied wurde zwischen den Messzeitpunkten für den Parameter HR-Decrement und HR-Recovery in beiden Gruppen gefunden.

Schlussfolgerungen: Die Ergebnisse zeigen keine Verbesserung der kardiovaskulären und autonomen Funktion innerhalb der ersten 5 Tage nach dem Eingriff. Nach 3 Wochen postoperativ wird eine Verbesserung der kardialen Funktion auf Grund der niedrigeren Rest- und Peak-Herzfrequenz angenommen. Eine Verbesserung bzw. Erholung der autonomen Funktion (keine Erhöhung von HR-Decrement und Recovery) konnte auch nach 3 Wochen nicht nachgewiesen werden. Es wird angenommen, dass die autonome Funktion eine längere Regenerationszeit als 3 Wochen benötigt.

Abstract

Introduction: Aortic stenosis is a chronic, progressive valve disease very common in the elderly population of the western world. If left untreated it leads to reduction of cardiovascular system (CVS) and autonomic function, left heart insufficiency, sudden cardiac arrest, syncope and ultimately premature death. Therefore, these patients sooner or later are in need for aortic valve replacement. New technics, such as the mini sternotomy, have been introduced in the past years and showed supremacy over conventional methods. Usually only hard end-points such morbidity and mortality are considered when evaluating patient outcome after these minimal invasive aortic valve replacement interventions. However functional parameters of CVS and autonomic system function could give useful insight of how recovery in these patients' manifests. So far cardiopulmonary exercise tests have not been used in early stages of recovery. In the literature there is thus no insight found on how exercise tests effect CVS and autonomic function parameters in these patients after recovering from minimal aortic valve replacement interventions.

Aims & Objectives: This study aims to investigate early changes in cardiovascular and autonomic function after aortic valve replacement surgery, by using submaximal cardiopulmonary exercise testing (CPET).

Materials & Methods: A sample of 10 aortic stenosis patients was matched to a heathy control group (n=10) and assessed with submaximal CPET at three times (pre-operative, 5 days' post-operative, 3 weeks post-operative). The assessed CVS parameters: rest HR, peak HR, HR recovery and decrement were compared between these three times by multivariate variance analysis. Pre-operative CVS parameters of the aortic stenosis group were secondly compared to the healthy control group. Post-operative, half the aortic stenosis patients (n=5) received β-blocker therapy with bisoprolol. Thus, the aortic stenosis group was split up and analyzed separately.

Results: Expected difference in CVS parameters between aortic stenosis and healthy control was slightly not significant. Further no significant difference was found for rest HR, peak HR, HR recovery and decrement between pre-operative and post-operative 5 days. 3 weeks' post-operative a significantly lower peak *(p=.002)* and rest HR (*p=.025*) was found in both β-blockaded and non β-blockaded aortic stenosis groups. However no significant difference between heart rate decrement in both groups was found.

Conclusions: Results indicate, that no improvement of CVS and autonomic function within the first 5 days of recovery takes place. Cardiac function improves within 3 weeks' post-operative (lower resting and peak heart rate). Autonomic function improvement however, might take longer than 3 weeks (no acceleration of HR recovery and decrement).

List of abbreviations

ACC/AHA: American Colleges of Cardiology/American Heart Association

AVR: aortic valve replacement

AVA: aortic valve area

AS: aortic stenosis

BP: blood pressure

CO: cardiac output

COi: cardiac output index

Bpm: beats per minute

CVP: central venous pressure

TPR: total peripheral resistance

ACh: acetylcholine

CPET: cardiopulmonary exercise test

CVS: cardiovascular system

ECG: electrocardiogram

EF: ejection fraction

HR: heart rate

LV: left ventricle

LA: left atrium

Max-CPET: maximal cardiopulmonary exercise test

Mini-AVR: minimally invasive aortic valve replacement

O2: oxygen

O2-pulse: oxygen pulse

PAPs: pulmonary hypertension

SM-CPET: submaximal cardiopulmonary exercise test

VCO2: carbon dioxide production

VO2: oxygen uptake

VO2 max: maximal oxygen uptake

VO2/HR: oxygen pulse

HHR: heart rate recovery

SSHR: maximal heart rate

DHR: heart rate decrement

PNS: parasympathetic nervous system

SNS: sympathetic nervous system

W: cyclin power output

Rpm: rounds per minute

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1. Introduction

1.1. Physiology of the cardiovascular system function

The cardiovascular System is the bodies tool for substance transport, it maintains a vital environment for every cell in its bond. Its main function is to support cellular respiration. The central structure a suction pump (the heart), a variety of blood vessels and a transportation vehicle (the blood), guarantee a constant supply with vital substances, such as oxygen and glucose, as well as disposal of waste for every tissue in the body. The mechanism with which the blood is pumped through the whole body is a very complex and adaptable system, influenced by extrinsic and intrinsic factors and regulated by the autonomic nervous system and renal hormones. In order to distribute the blood constantly, a stable blood flow through arterial pressure is necessary. Likewise, the system needs to be able to adapt the pressure to different tissue needs, under changing circumstances such as stress from exercise. Thus, the body tries to keep the cardiovascular system leveled by changing peripheral resistance, blood volume, heart frequency and contractility [(2), p182].

1.1.a. The heart as the initial point

The contraction of the four- chambered heart, which consists of two atriums and two ventricles, is initialized and spread through nerve cells, the conductive system [(2), p185]. It consists of its main pacemaker the sinoatrial node, which coordinates every cell to a sufficient, rhythmical, contraction. Further the atrioventricular node, the His bundle and its branches and the Purkinje fibers [(2), p185]. Emanating from the SA node, the electric stimulus runs through the conductive system and spreads the depolarization, using gap junctions, over the hole heart. Even though all fibers of the conductive system can depolarize automatically the SA node is the highest and fastest instance because it depolarizes more often with about 100 impulses per minute compared to the AV node with 50 impulses [(2), p185]. The SA node therefore is the main pacemaker. If it does not fire or impulses are blocked the AV node can take over as pacemaker. The SA node is under influence of the autonomic system, in rest PNS activity is predominate over SNS, therefore resting heart frequency lays at about 70 bpm (2).

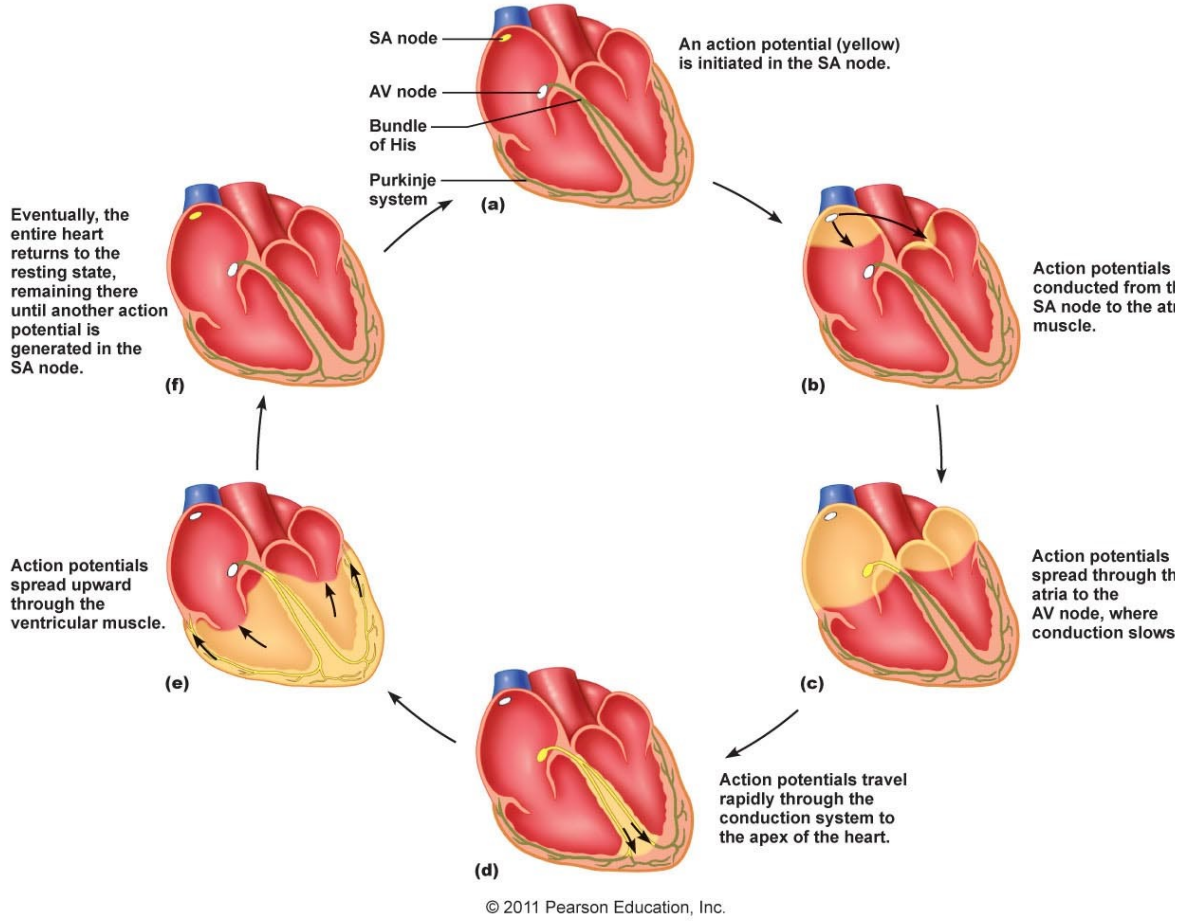

Figure 1. shows the spread of action potentials over the myocardium. Taken from (http://droualb.faculty.mjc.edu/Course%20Materials/Physiology%20101/Chapter%20Notes/Fall%202011/chapter_13%20Fall%202011.htm)

The depolarization not only triggers the myocytes in the heart to contract, but is also conducted via body fluids to the body surface. Where it can be measured in potential difference with ECG. The ECG measures the electrical conduction over the heart. It shows the depolarization waves, spreading the excitation over the myocardia and the repolarization wave.

1.1.b. Vascular system function and blood pressure

The heart contributes the blood to every cell of the body via the vascular system. It consists of a high- pressure and a low- pressure system. The high- pressure system is made up of left atrium, left ventricle and the arteries, which transport the oxygen and nutrients loaded blood in the periphery. Guided through arterioles and capillaries finally reaching every cell, the blood then runs back via the low- pressure system through venules and veins reaching the right atrium and ventricle at the end [(3), p157]. The venous system also serves as blood reservoir, it is holding about 64% of the blood volume [(3, 6), p158]. Under low pressure the

body can mobilize this volume and return it back to the heart, to increase stroke volume and thus blood pressure [(3), p158].
With every beat, the heart pumps blood in the circulation, the pressure in the arterial tree varies. While the pressure in the aortic arch averages 100mmHg in middle, in capillaries it is only at about 17mmHg and once returned back to the right ventricle it is almost down to 0mmHg. The pulmonary artery also has a fairly low pressure for an artery at 16mmHg in middle, simply because the blood has to flow slower, in order to adequately get oxygenated in the lungs capillaries [(3), p158]

Since the heart as to fill up, before pumping blood onwards, it works in two cycles. The diastole and the systole. This cardiac cycle leads to a pulsatile arterial pressure. Were in systole the pressure in the aortic arch is at 120mmHg in young healthy adults, the diastolic pressure is at only 80mmHg. The average of the pulsatile pressure is mean arterial pressure and is commonly used reference value (2).

To maintain a constant blood flow and therefore constant supply for all tissues, the body has a way of keeping the capillary pressure constant. By limiting the pressure pulsation through the arterial systems compliance [(3), p168]. Hence the aortic wall with its high compliance gets stretched by the blood flow wave and absorbs part of the pressure, to sustain a constant capillary blood flow. The lower the compliance the higher the pulse pressure curve, leading to arterial hypertension. This pathogenesis can especially be seen in patients with arteriosclerosis (2).

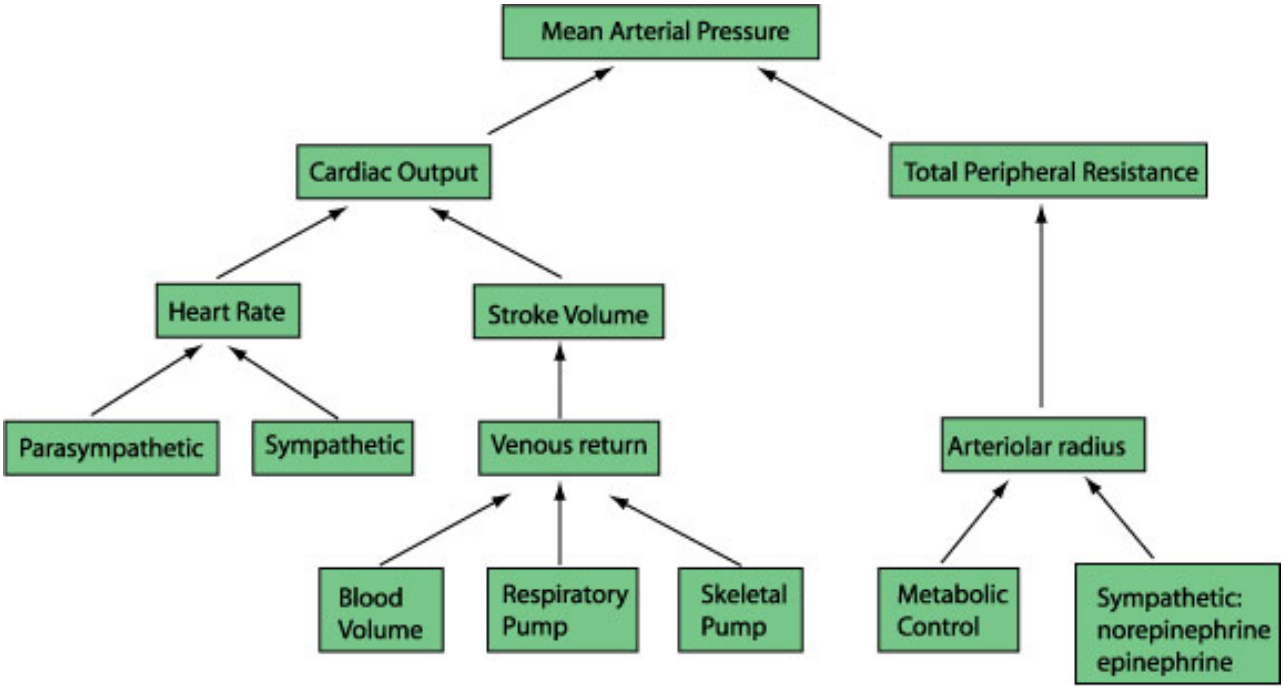

Figure 2. Factors determining mean arterial pressure. Taken from: (https://isaacsondianaphysiology.wikispaces.com/file/view/MAPfactors.jpg/211664766/MAPfactors.jpg)

As mentioned above to maintain a constant blood flow, a constant blood pressure is inalienable. The main value of the CVS is mean arterial pressure. It is the marker, that CVS function is regulated by and reacted on. Arterial pressure is defined as “force exerted by the blood against any unit area of the vessel wall” [(3), p162: line 23-24], it is historically measured in mmHg.

It is determined by the amount of blood being pumped per minute (CO) and the resistance against whom the heart has to work (TPR) [(3), p168]. Shown in the formula below.

MAP= CO*TPR

Cardiac output is defined as the quantity of blood that left and right ventricle convey per minute and ranges from 5 to 6 L/min (4). It is calculated from stroke volume multiplied with heart rate.

CO= SV* HR

Heart rate is under the influence of sympathetic and parasympathetic system, known as the autonomic system. In rest HR is therefore determined by MAP, during exercise however it depends on SV via Frank-Sterling mechanism (2). This will be discussed in the following chapters.

The stroke volume is the quantity of blood pumped during every heart stroke, being the result of end- diastolic volume (130ml) minus end- systolic volume (50 ml), it is about 80ml (2) p202. Shown in the formula below.

SV= end-diastolic volume – end-systolic volume

It is determined by the amount of blood the heart receives back through venous return. Venous return depends on the volume of blood in the body and the activation of muscle and respiratory pump (3).

In order to compare the cardiac output of individuals with different physical appearances and ages the bodies surface is considered and cardiac index can be determined, normally it is about 3,2 L/min/m². The importance of these measurements get comprehensible, if one considers them to assess the efficiency of the heart or the severity of cardiac diseases, such as the aortic stenosis (AS) [(5), p1453]. Another important parameter regarding diagnosis and evaluation especially of severe aortic stenosis, is ejection fraction. Which is the percentage of end- diastolic volume, pumped into the aorta per stroke, it is about 60% [(2), p202] in heathy individuals and lower in AS patients.

Total peripheral resistance is the total of all arterial radiuses, it can be calculated from blood flow and pressure differences (2). The arterial radius is also controlled by the autonomic system and local tissue needs.

The factors to determine MAP are shown in Figure 2. and are discussed in detail in the following chapter.

1.1.c Intrinsic regulation of blood pressure

The amount of blood that the heart pumps is determined by tissue needs. To meet these needs two basic principles are applied. The intrinsic regulation of blood pumping, which is determined by changes in blood volume returning to the heart and the myocardial contractility. Alongside the extrinsic control of inotropy (contraction force) and chronotrophy (heart rate) and vascular resistance through the autonomic system (3).

The intrinsic regulation is the hearts ability to pump all blood that comes back over venous return [(3), p110]. Through more venous return the myocardial fibers experience a greater stretch during diastole. Greater stretching causes a more sufficient overlapping of actin and myosin filaments and therefor they can contract with more force. The venous blood returned, generates a certain pressure in the ventricles, depending on how much volume is return, the tension on the ventricle wall rises. This is known as the preload [(3), p110]. The force or the ventricle tension that the ventricles need to build up to eject the stroke volume against the pressure in the aorta is called the afterload. [(3), p109]. This principle is known as the Frank-Sterling-mechanism.

1.1.d. Extrinsic blood pressure regulation and heart rate control through autonomic system regulation

The extrinsic blood pressure regulation is being carried out by the autonomic system. It consists of sympathetic and parasympathetic fibers. Since blood pressure is a product of stroke volume, heart frequency and total peripheral resistance, the autonomic system has ways of changing these three parameters, to keep constant pressure even under changing tissue needs. Sympathetic and parasympathetic fibers have opposite effects one heart and blood vessels.

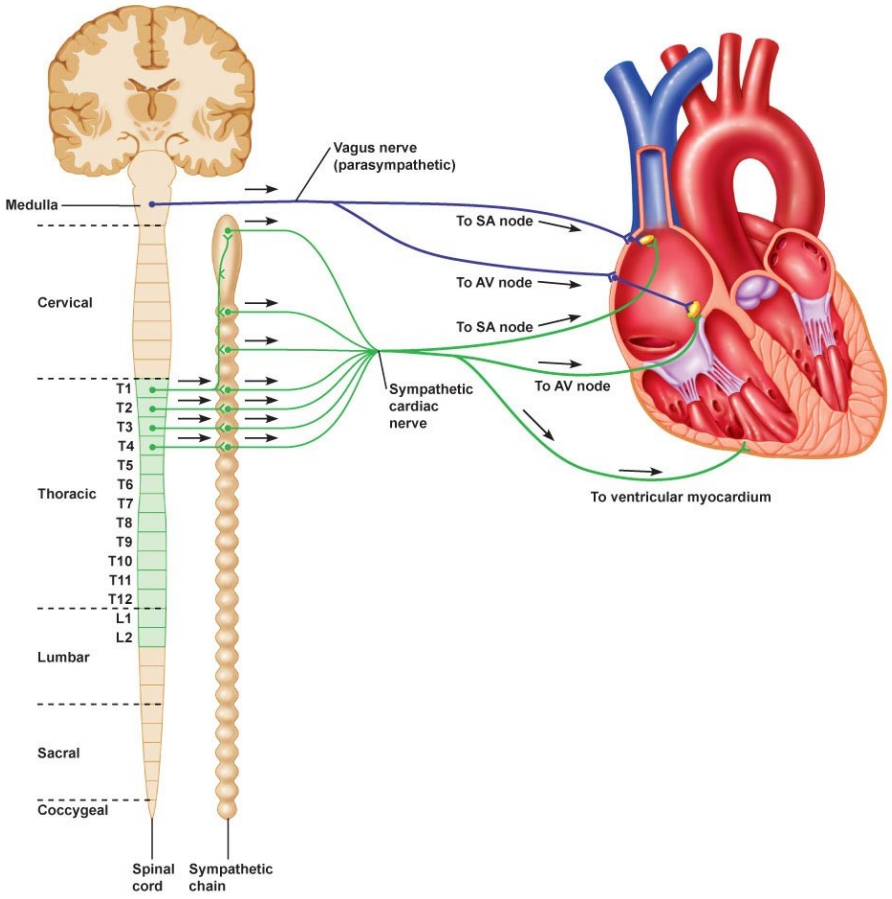

Figure 3. shows autonomic system innervation on the heart. Taken from: (http://droualb.faculty.mjc.edu/Course%20Materials/Physiology%20101/Chapter%20Notes/Fall%202011/chapter_13%20Fall%202011.htm)

1.1.d.a. Sympathetic nervous system

The center peace of the autonomic system is the vasomotor center in the medulla oblongata and the pons [(3), p216]. from here sympathetic nerve fibers run parallel of the vertebral column, the sympathetic trunk. In the upper thoracic region preganglionic nerves of the spinal cord connect with postganglionic fibers from the sympathetic trunk to form the sympathetic cardiac nerve. It innervates SA, AV node and myocardium, where sympathetic action potentials lead to rise in heart rate and contractility (2, 3).

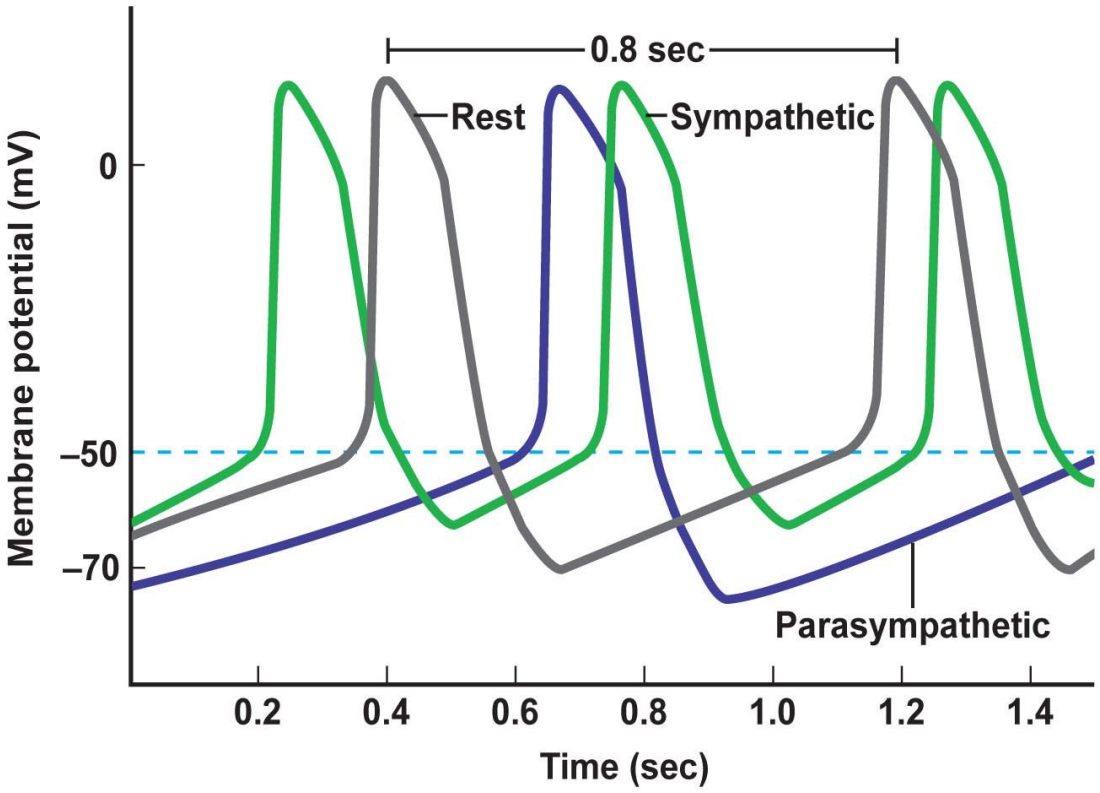

Figure 4. shows sympathetic vs. parasympathetic vs. rest action potentials in the SA node. Sympathetic action potentials being three times higher compared to parasympathetic action potential, leading to increased HR. Taken from: (http://droualb.faculty.mjc.edu/Course%20Materials/Physiology%20101/Chapter%20Notes/Fall%202011/chapter_13%20Fall%202011.htm)

Further ganglions emerge from the sympathetic trunk parallel to the vertebral column and innervated blood vessels, increase resistance by vasoconstriction. Leading to centralization and less perfusion of the kidneys, skin and intestines. In skeletal muscles and the liver, sympathetic impulses dilatate innervated arterioles and capillaries, leading to higher local blood flow (2, 3).

The sympathetic nervous system operates via several neurotransmitters, such as noradrenalin and dopamine and hormones, such as adrenalin. For blood pressure control three types of adrenergic receptors can be differentiated.

α1 receptors, located on vascular smooth muscles cells mediate vasoconstriction or dilatation of small arteries and arterioles in skeletal muscles and the liver. This causes increase of TPR in skin and intestines and decrease of TPR in muscles and liver. Resulting not only in more or less local blood flow but also influence MAP and afterload (3).

Secondly β1 adrenergic receptors, located in the ventricle myocardium, through which contractility and therefore SV can be increased. Further in the SA node located β1 adrenergic receptors mediate heart rate increase as high as 180-200 bpm. HR increase via

sympathetic system however takes about 6-8 heart cycles and is therefore compared to parasympathetic withdrawal the slower way (5, 6). In the end cardiac output rises through rise in stroke volume and heart rate [(3), p120].

In the venous system sympathetic activity mobilizes blood volume from venous capacity. Through activation of the muscle pump (by compressing the veins) and respiratory pump (causing the blood getting sucked back into the atria), leading to more venous return (2).

The sympathetic nervous system also carries fibers that cause vasodilatation in muscle cells and liver to fill the needs of nutrients during stress or exercise. This is being carried out by adrenalin, circulating in the blood and binding to β2 adrenergic receptors. Neurotransmitters and hormones used by the autonomic system have different affinities to the various adrenergic receptors. While adrenalin binds to adrenergic α1, β1 and β2 receptors, noradrenalin is affine to α1 and β2. Since α1 and β2 are mostly located in blood vessels noradrenalin is the stronger vasoconstriction neurotransmitter. Heart rate is therefore mostly

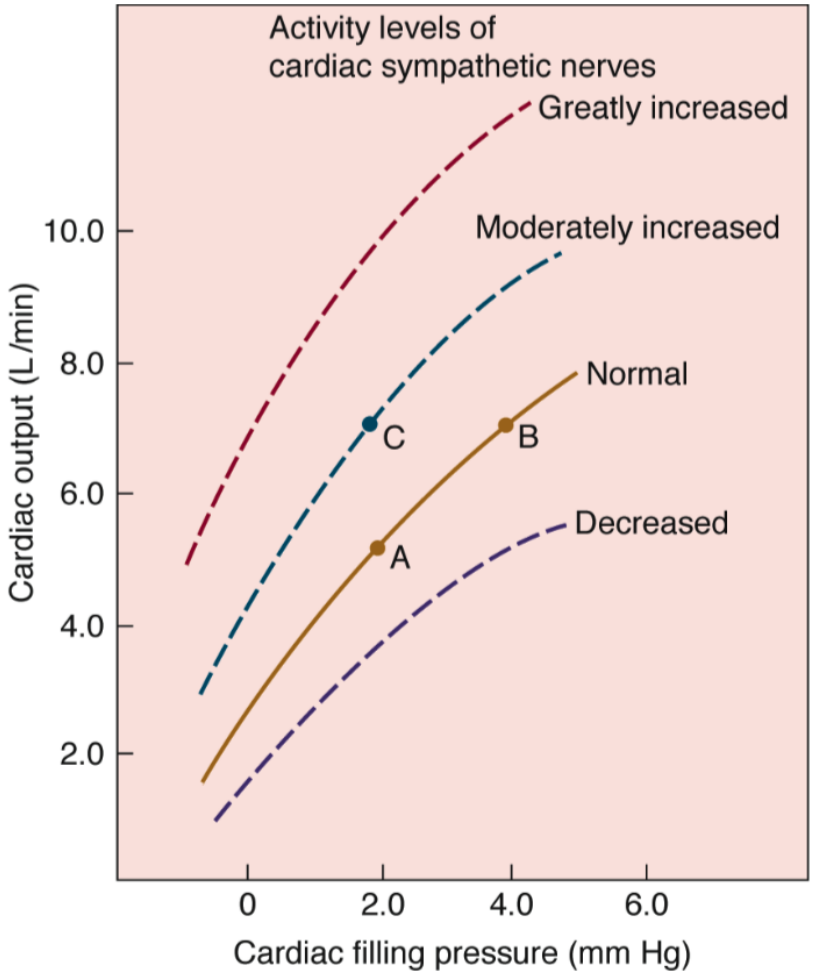

Figure 5. Shows CO changes under the influence of sympathetic activity, greater sympathetic activity and preload leading to higher CO. Taken from (http://d1yboe6750e2cu.cloudfront.net/i/7124e2959a6d93781e56a46b14608546375c27d7)

under hormonal control by adrenalin with similar effects as sympathetic action potentials (rise in HR). Furthermore, thyroid hormones, insulin and glucagon also increase cardiac contraction.

Autonomic system regulation of the arterial pressure acts very quickly. Within one to two cardiac cycles the HR rises by parasympathetic withdrawal. Followed by sympathetic activation, which responds slower within 6 to 8 cardiac cycles. Triggering vascular tone, vascular resistance, myocardial contractility as well as HR acceleration simultaneously. Constricting of most arterioles leads to rise in TPR. Compression of veins leading to higher venous return and rise in CVP. Ultimately stimulation of β1 receptors in the myocardium and SA node, increases SV and HR, hence CO increase (3, 6, 7). Figure 5. Shows that the main factor increasing CO, beside rise in cardiac filling pressure via Frank-Sterling mechanism is actually rise in sympathetic activity.

1.1.d.b. Parasympathetic nervous system

The second division of the autonomic system is the parasympathetic center, located in the brain stem and conducts its signals over the vagal nerve. It operates with muscarinic cholinergic receptors that are triggered by acetylcholine (ACh). These receptors are located in the SA and AV node mediating signals to lower heart frequency, by decreasing the frequency of action potentials. It cannot be found on vascular smooth muscle cells (6, 7).

The autonomic system in general combines sympathetic and parasympathetic actions in an alternating way by sympathetic increase and parasympathetic decrease and the other way around. If there would not be any stimulation the resting HR would be much higher at about 100 bpm. This is due to parasympathetic domination during rest (3).

1.1.d.c. Sensing blood pressure through Baroreceptors

The autonomic system always tries to keep blood pressure stable or at least prevent it from increasing too far or drop to low. If an increase in preload leads to an increase of CO through Frank-Starling mechanism a rise in MAP accrues. The autonomic system senses this with pressure receptors laying in the vascular walls of arteries, especially in the aortic arch and the carotids. It counteracts on blood pressure increase over its negative feedback system.

A rise in pressure leads to greater stretch of the artery walls, the pressure receptors are able to sense very small changes in wall tension and give feedback over the autonomic system. The signals are either coming from receptors in the aortic arch, running over the vagal nerve or coming from receptors in the carotis interna. Finally, the signals reach the nucleus tractus solitarius in the medulla. Since the baroreceptors are very sensitive to pressure changes, even small shifts above a certain pressure levels can cause rapid firing. In the aortic arch

these levels are above 100mmHg, while in the sinus caroticus above 50-60 mmHg [(3), p219].

Once the transmitted signals reach the medulla oblongata, they cause inhibition of the vasoconstriction center as well activation in vagal parasympathetic center. This leads to a decrease in vasoconstriction tonus and thus decrease in TPR. Also the activation of the parasympathetic system causes a decrease in heart rate and contractility, leading to less cardiac output and a reduction in MAP, respectively preventing MAP to increase further [(3), p220].

This baroreceptor monitoring system not only reduces MAP but of its nature being a negative feedback system, baroreceptors decrease activity if they sense a low blood pressure. Meaning through their decreased activity the inhibition of the vasoconstriction center and excitement of the parasympathetic activity are diminished. Through this buffering function, the autonomic system can not only monitor pressure changes but react in both directions regulating pressure in an up or downwards direction. This reaction mechanism is called the baroreceptor reflex and allows maintenance of constant blood pressure throughout. The baroreceptor reflex is exemplified in figure 6.

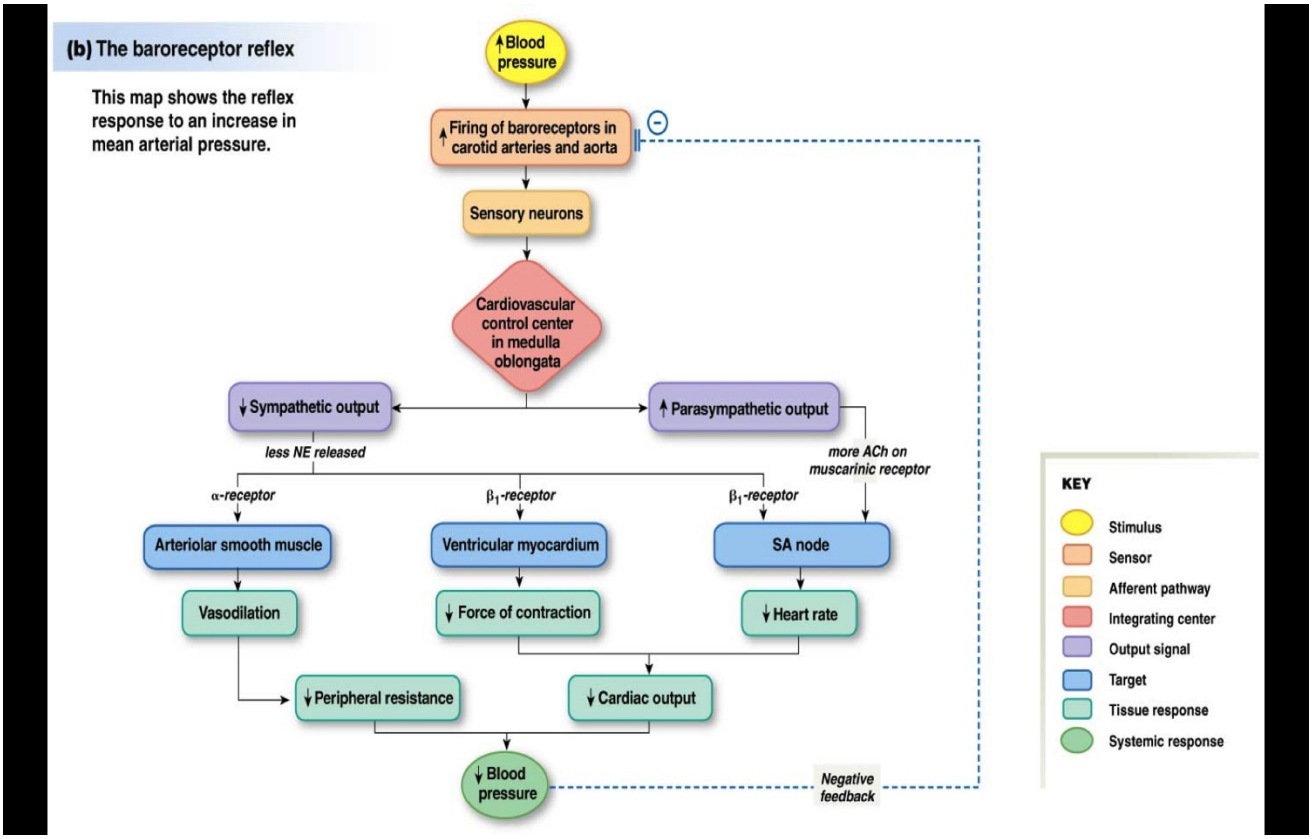

Figure 6. Negative feedback blood pressure control by baroreceptors. Taken from (https://classconnection.s3.amazonaws.com/540/flashcards/1654540/png/reflex1340664561440.png)

1.1.d.d. Chemoreceptors

Another major role in blood pressure control is played by chemoreceptors. The conduction and effect in the medulla, being vasoconstriction inhibition and parasympathetic excitement is nearly the same as the baroreceptors. However, the difference being, that these chemo sensitive cells are not as potent as baroreceptors. The anatomic location is similar to the baroreceptors, in the bifurcation of the carotids (carotid body) and the aortic body attached to the aortic arch. The chemoreceptors sense a lack of oxygen, rise of carbon dioxide and hydrogen ions, however the reflex is not triggered at levels above 80mmHg and thus it is not a powerful pressure controller [(3), p220].

1.1.e. Long-term blood pressure regulation through hormones

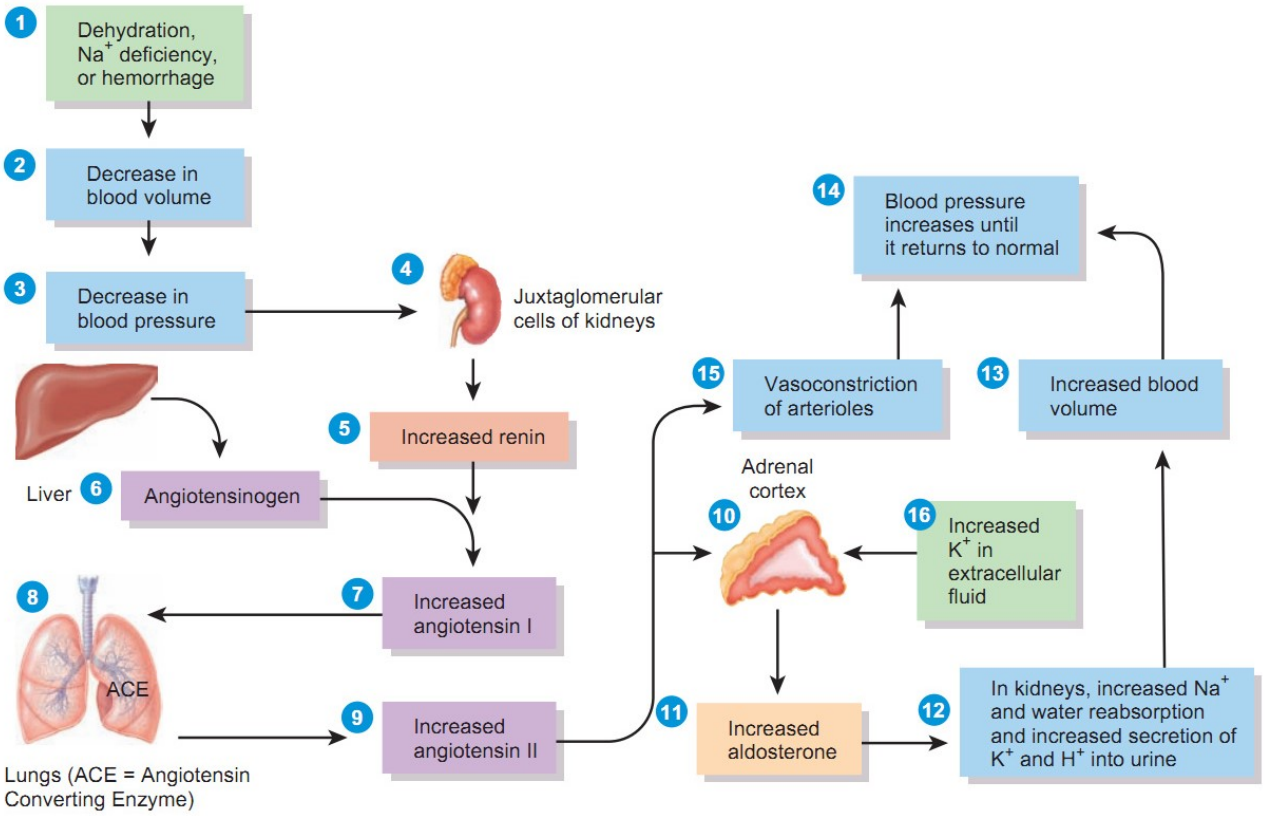

Figure 7. shows long term blood pressure regulation. Taken from: (http://antranik.org/wp-content/uploads/2012/05/renin-angiotensin-aldosterone-reflex-system.jpg)

Short-term blood pressure has been discussed in detail, what effects regulated blood pressure in the long run are shown in Figure 6. by the renin angiotensin aldosterone system (RAAS). If the body loses water or natrium, through dehydration or hemorrhage, the blood volume decreases. Less blood volume means less venous return to the heart and hence less preload resulting in impaired stroke volume. A decrease in SV brings about a drop of MAP and therefore less perfusion of peripheral tissues such as the kidneys. A decrease blood flow through the kidneys is sensed by the juxtaglomerular cells, by measuring natrium chloride,

and stimulates renin release. Renin converts angiotensinogen, produced in the liver, to angiotensin I which again is converted into angiotensin II by angiotensin converting enzyme mostly in the lungs. Angiotensin II is a strong vasoconstriction mediating hormone on arterioles [(3) p212], causing rise in total peripheral resistance and thus rise of MAP. Furthermore, angiotensin II increases aldosterone segregation from the adrenal cortex. Aldosterone is a very potent mineralocorticoid that stimulates natrium and water reabsorption and potassium secretion. This mechanism leads to enhanced blood volume and thus rise MAP (3).

1.2. Cardiovascular system function under exercise

Because oxygen is the limiting substance for muscle contraction, muscles need constant supply of oxygen. More blood and more oxygen need to be transported by the cardiovascular system when consumption of the muscles rises dramatically during exercise up to 10-15-fold in untrained young healthy humans and up to 20-fold in elite endurance athletes, compared to resting levels (4). The CVS job during exercise is to constantly supply the muscles and nutrients.

1.2.a. CVS function during exercise

Oxygen demand rises under exercise because skeletal muscles need oxygen to convert glucose into usable energy (ATP). It is the bodies main energy source, called aerobic glycolysis. To increase oxygen uptake, the body has two ways: Incrementing respiration and oxygen perfusion through the lungs, incrementing blood transportation. In order to transport more blood, the CVS increases CO. As discussed earlier CO can be augmented by either increasing heart rate or SV. Commencing exercise an increase in SV, mediated through Frank Sterling mechanism, accrues first. Secondly a rise in heart rate accrues to increase CO even further. Therefore, in young healthy individuals heart rate increases up to 200 bpm during maximum exercise (8). This is achieved through sympathetic nerve activity on the heart as well vagal tone decrease (9). Whereas vagal withdrawal is very fast and effects the heart rate within one beat, sympathetic nerve activity is slower and takes a few seconds. Furthermore, higher muscle perfusion is achieved by increase in stroke volume commencing exercise. Due to enhanced myocardial contractility and higher venous return through the muscle pump as well as rise in respiration. This can lead to cardiac output of 20 l/min and up to 40 l/min in elite athletes, compared to resting values at 5 l/min (4). If the workload increases further, the body needs to produce an even higher CO. To achieve that goal, heart rate rises further. Figure 8 shows heart rate and Oxygen uptake (VO2) response to exercise. VO2 is the amount of oxygen the body is able to absorb and transport to cells in need per minute. Oxygen capacity depends on three factors, respiration capacity, CO (transportation capacity) and mitochondrial capacity (how much O2 can actually be consumed). The limiting

factor is in general transportation capacity. Since CO depends on SV and heart rate, an increase in both takes place during exercise (10).

Figure 8 shows the correlation between heart rate and oxygen capacity during constant

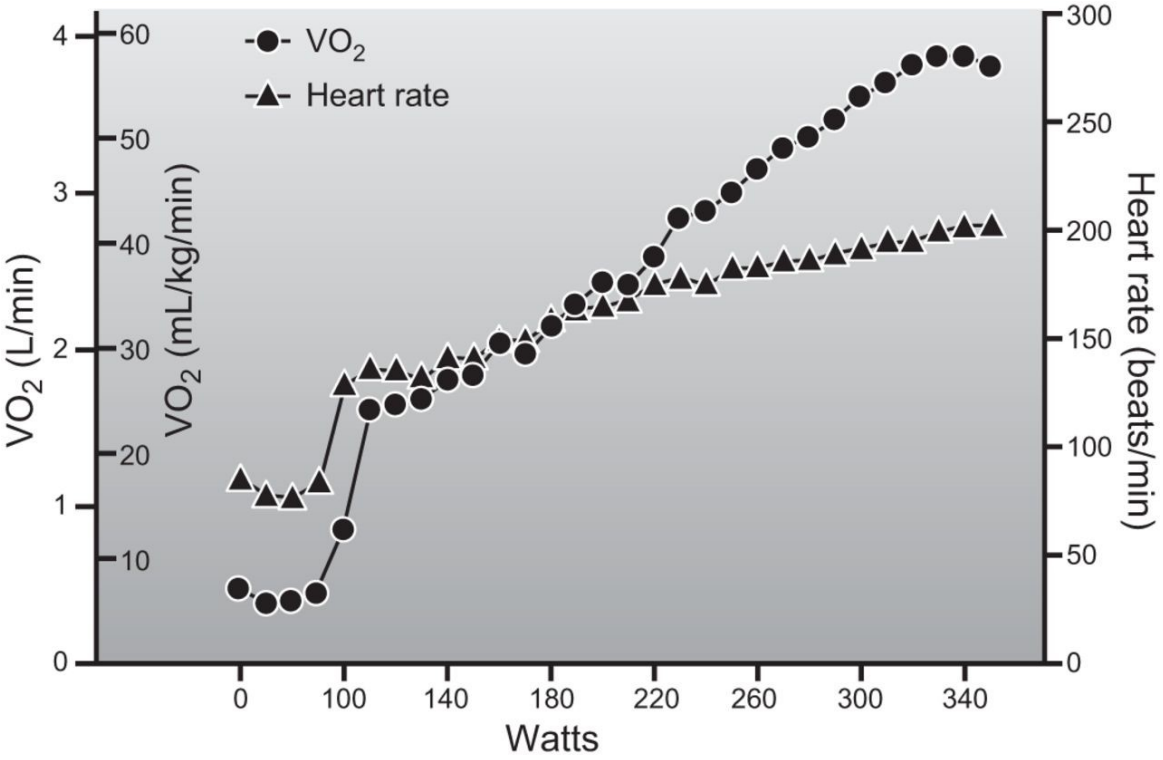

Figure 8. Analogic rise of HR and VO2 during constant workload increase in watts. [20]

workload increase. Commencing exercise there is a similar increasing trend for VO2 and heart rate, indicating that heart rate in sinus rhythm increases linearly with workload and oxygen demand. At a certain workload there is a rapid VO2 slope increase compared to heart rate curve. This phenomenon is due to more efficient respiration and an increase in SV. Once the heart rate cannot be increased further, VO2 also hits a plateau and even decreases a little. This shows the limiting factor is transportation capacity, ultimately maximal heart rate as an indicator of maximal oxygen capacity (10).

Not only skeletal muscles need more oxygen under exercise but also myocardial fibers. Exercise physiologically stimulates myocardial oxygen consumption, because of ventricular work increment. In order to deliver the extra work, the hearts own perfusion needs to be enhanced. Therefore, coronary blood flow rises up to 5fold (11).

1.2.b. Autonomic system regulation during and after exercise

During rest the parasympathetic nervous system is dominated over the sympathetic (3) and heart rate regulation is determined by MAP. During exercise however, heart rate regulation is determined by stroke volume and ultimately pre-load via Frank Sterling mechanism. Meaning more pre-load leads to higher CO through rise in SV. In particular, at the beginning of exercise

SV makes up for the bigger part of CO, it reacts within one heart cycle. Since all the blood that is returned to the heart is transported along (3), only if workload keeps progressing the heart rate also rises further mainly by parasympathetic withdrawal. If the exercise continues into a higher intensity the sympathetic nervous system is activated resulting in tachycardia. It is therefore a combination of parasympathetic withdrawal and sympathetic activation (8). But even under high-intensity exercise total parasympathetic withdrawal does not occur (12). After completing an exercise of moderate or vigorous intensity the heart rate decreases. The rate at which this occurs depends on the relation between PNS and SNS and is referred to as heart rate recovery. It was observed that the recovery of the heart rate is mediated through a coordination of parasympathetic reactivation and sympathetic withdrawal. Whereas the parasympathetic reactivations occurs faster and plays the more important role in lowering heart rate (12, 13). HHR is therefore a marker for vagal reactivation, making heart rate recovery a marker of parasympathetic (14, 15). During submaximal exercise the HRR is faster compared to maximal exercise do to less sympathetic activation (16). HRR can be calculated as the difference between peak heart rate and heart rate during the recovery phase. It is sometimes referred to as heart rate decrement (DHR).

A delay in the HRR or lower DHR is assonated with chronotropic incompetence resulting from autonomic imbalance or an compromised parasympathetic reactivation (17). This impaired parasympathetic reactivation also diminishes the positive antiarrhythmic effect post exercise on the heart (13). A decrease in heart rate recovery is further highly associated with cardiovascular disease such arteriosclerosis and all- cause mortality (18) and is a parameter that is liked to autonomic imbalance, a low fitness form and overall mortality (8, 19, 20).

1.2.c. Exercise to evaluate cardiovascular system function

HRR is a noninvasive and relatively simple tool of assessing autonomic system activity and when reduced can be an indicator for autonomic imbalance (8). Physical exercise increases heart rate recovery, and since it is an effective parameter to assess autonomic tone it can be used to evaluate patient outcome (21). A study form 2003 using treadmill exercise to assess 6546 patients over 10 years, found that anomalous heart rate recovery of <12 bpm leads to a high increase of mortality risk (18). A study from 2005 including 5317 healthy individuals came to the conclusion, that HRR and elevated resting heart rate and a low maximal heart rate is highly associated with sudden death (20).

This leads to believe that heart rate recovery, rest heart rate and peak heart rate could provide additional prognostic value for AS patients and should be assessed whilst exercise testing.

1.2.d. Blood pressure regulation during exercise

If rise in HR and SV, is still is not enough to meet the requirement of risen oxygen consumption in the muscles, the cardiovascular system also uses blood flow redistribution. The body does so by redistributing the blood from visceral organs such as kidney, liver and inactive muscle (22, 23). Were blood flow can fall to 25% of flow during rest. This is being mediated by sympathetic vasoconstriction. The redistributed blood flows to skeletal muscles and coronary arteries were flow rises three to four times compared to resting flow (11). Mean arterial pressure rises only little during moderate dynamic exercise as it is being regulated by the baroreceptors. It is the job of the autonomic system to keep MAP stable and prevent it from dropping, which can occur during vasodilatation in skeletal muscles (24). Therefore, autonomic system activity increases during exercise by increase in sympathetic nerve traffic, dumping in noradrenalin (25). The baroreceptors are essential to rise in sympathetic activity and arterial pressure commencing exercise. Also, the baroreceptors are necessary to oppose the contrary effects of metabolic dilatation mediated through chemoreceptors and sympathetic vasoconstriction (25).

Even though CO rises during moderate exercise, TRP declines caused by vasodilation and most of the CO flows to the skeletal muscles, to keep working muscles perfused adequately (26). This can during exercise or stress testing even lead to hypotension, especially in patients with left outflow tract obstruction, such as aortic stenosis (27). The hypotension can be so drastic that it can lead to cerebral hypoperfusion and syncope (11, 28). In this case the autonomic system is needed to maintain tonic sympathetic vasoconstriction to prevent hypotension by restraining muscular blood flow (29, 30). In patients in which this sympathetic vasoconstriction does not occur, this leads to a drop in MAP (31). In healthy subjects, MAP starts to rise dramatically once the workload increases over a certain limited. Especially, systolic blood pressure increases up to 200 mmHg (32). In conclusion aortic stenosis patients should because of possible trop in MAP not be exposed to maximal exercise testing but submaximal.

1.3. Aortic Stenosis

Aortic stenosis, is defined as the narrowing of the aortic orifice below its usual aortic valve orifice area 3.0 to 4.0 cm² (37). Being a chronic progressive valve disease, it is rather common in older people and makes up for 34% of all valve diseases in Europe (37) It is therefore the most frequent heart valve disease in Europe (38). A significant rise in prevalence is to be seen, especially in its most common form of aortic sclerosis with 20% in patients between 65-75 years, 35% in patients 75-85 years and even 48% in patients above 85 years (1).

The aortic stenosis is a disease of the valve leaflets, whose three major causes are: congenital bicuspid valve, calcific aortic valve and rheumatic valve disease (37). The AHA

guidelines rate the severity of AS is depending on the aortic valve area: > 1.5 cm² is considered mild, 1.0 to 1.5 cm² is considered moderate and < 1.0 cm² considered as severe (39).

Calcific aortic valve is currently thought to have a very similar pathogenic mechanism as atherosclerosis (1). Where an early sub-endothelial plaque on the aortic side of the leaflet develops due to an infiltration of inflammatory cells, such as macrophages and T-Lymphocytes and oxidized LDL (1)

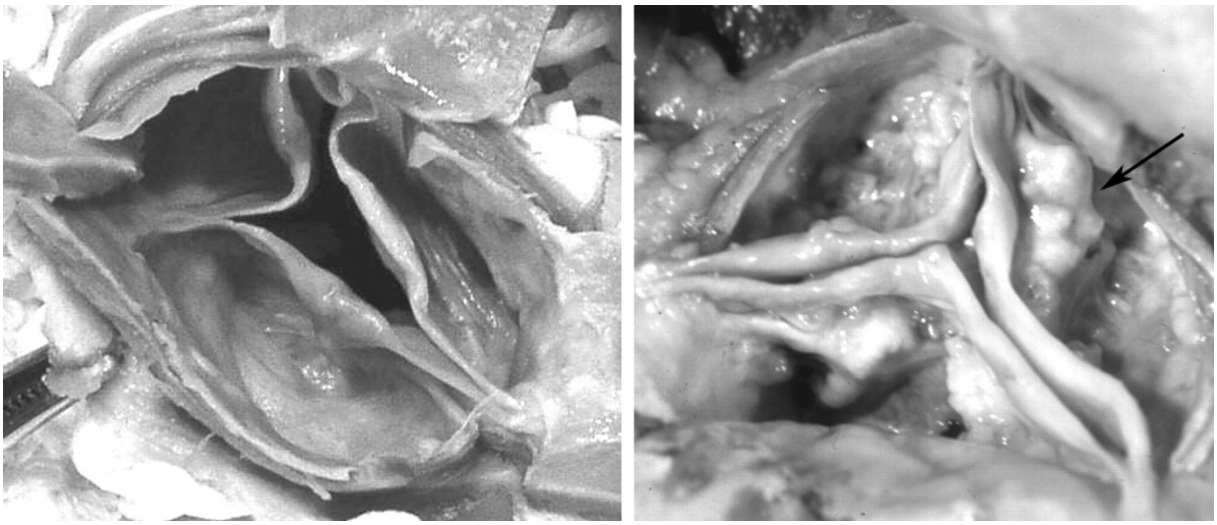

Figure 9. shows Figure 1. Gross specimen of minimally diseased aortic valve (left) and severely stenotic aortic valve (right). In the severely stenotic valve, there are prominent lipocalcific changes on aortic side of valve cusps (arrow), with sparing of commissures (38).

While patients with mild AS normally stay asymptomatic (40). Symptomatic patients sooner or later are in need for Aortic valve replacement surgery, if not they have a high risk of premature death (41).

1.3.a. Reduction of CVS function

Severe AS commonly presents itself with direct symptoms like chest pain, shortness of breath, syncope and sudden cardiac death or more indirect symptoms like rise in left ventricle mass (41). The reason for ventricle mass growth gets understandable considering the cardiac cycle.

It is composed of two phase's systole and diastole, in which the ventricle alternatingly contracts and relaxes. During mechanical systole, the ventricles contract and the semilunar valves are open. Blood gets ejected in aorta and pulmonary artery (2), p199]. If the valve opening area is reduced the outflow of the blood is restrained and the stroke volume impaired. In mild AS the reduced SV can be compensated with rise in heart rate to generate an adequate cardiac output. The obstruction that the stenosis creates, causes concentric

hypertrophy of the left ventricle. The rise in muscles mass leads to less efficient contractility during systole (systolic dysfunction) (42) as well as less elasticity during diastole (diastolic dysfunction) (43). The pressure gradient caused by the stenosis can also be used to classify AS severity: Gradient < 40mmHg being mild and with > 120 mmHg being very severe. The narrower the orifice area, the more gradient between ventricle and outflow tract meaning more ventricle contractility is needed to produce and adequate SV. The concentric hypertrophic ventricle has a worse contraction ability than a healthy one. In serve AS the impaired SV leads to reduced aortic pressure wave and therefore a lower MAP (37, 1, 5). Ultimately the body tries to always produce an adequate CO, therefore an increase of resting heart takes place in AS patients (SV*HR=CO). Higher resting heart rate is thus associated with greater AS progression rate especially in elderly patients (44).

1.3.b. CVS response during exercise in AS patients

During exercise the ventricle can, in mild and moderate AS adapt CO to the higher need. Whereas in severe AS the ventricle cannot do so, which can lead to a dangerous drop in MAP. Also, the perfusion of the coronary arteries, since their orifices are located directly behind the aortic valve, can be reduced caused by the pressure gradient. This gains special importance since the concentric hypertrophic ventricle has a higher oxygen demand. These two effects cause a disproportion of oxygen supply and demand and can lead to angina pectoris and ventricular fibrillation. (37, 1, 5)

Further pathophysiologic effects of AS are shown in a study from 2012, that AS correlates highly with autonomic imbalance, particularly in moderate to severe AS (45). The study further suggests researching the prognostic value of autonomic imbalance in AS patients. Autonomic imbalance presents itself, besides other limitations, with incompetence of the autonomic system to adapt the heart rate appropriately. This is caused by disbalance between sympathetic over activity and parasympathetic under activity, resulting in slower heart recovery after exercise (46). This can be seen in a reduction in HRR and lower maximal heart rate in AS patients (47). Also, lower HRR was proven to be a predictor of death and or need for AVR intervention (47). Autonomic imbalance caused by AS normalizes within one year after AVR (48).

To counteract these severe effects and symptoms for many patients aortic valve replacement is the best treatment decision (41). Of all the 50.000 aortic valve replacements performed annually in the US, aortic stenosis makes for the largest number (37).

1.4. Surgical treatment of aortic valve stenosis

As discussed above for many patients, especially with severe AS aortic valve replacement (AVR) is the only life progressing option. It increases patient life quality and reduces the mortality and morbidity (39). Conventional aortic valve replacement is carried out about 275.000 times a year worldwide (39) and is conducted via full sternotomy and cardiopulmonary bypass (49). During the last decade, however several minimally invasive alternatives to the full sternotomy have been performed more frequently, such as the right anterior mini-thoracotomy and the upper mini-sternotomy (39). Minimally invasive AVR (mini-AVR) from the upper mini-sternotomy approach is executed via hemi sternotomy, using various skin incisions, such as J- or L-shape (49).

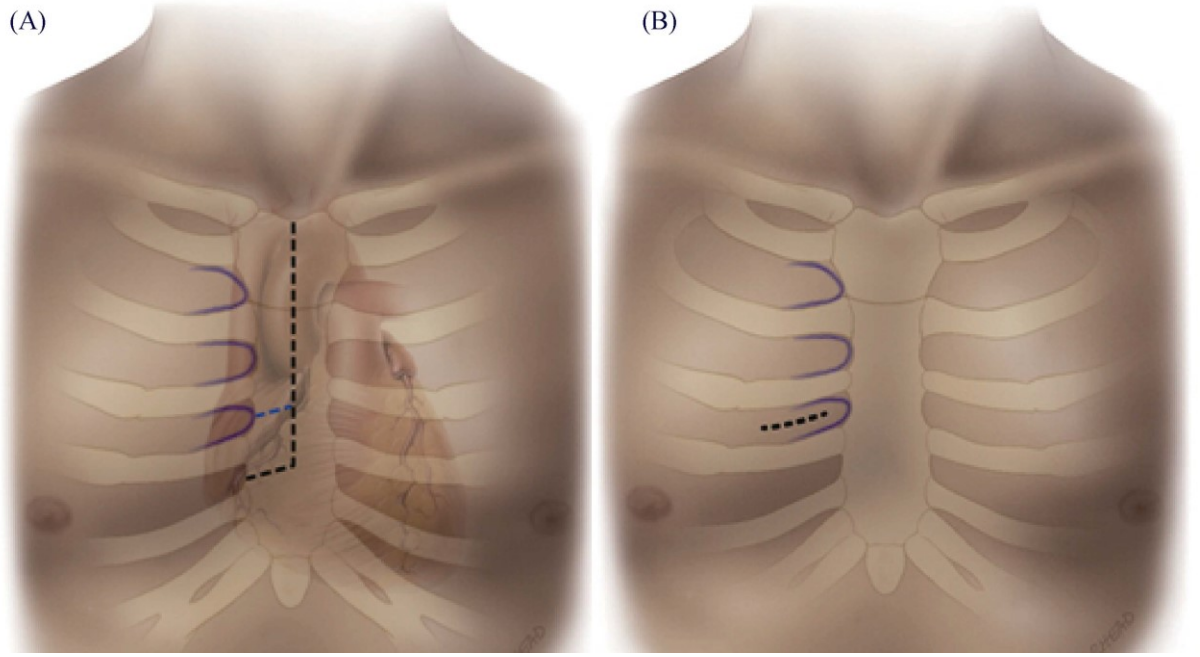

Figure 10 Schematic drawing of the skin incision executed during J mini-sternotomy into the right fourth or third intercostal space (A) and during right anterior thoracotomy incision in the third intercostal space (B) (38).

Compared to conventional AVR, mini AVR, both mini-thoracotomy and mini-sternotomy have shown to be superior, by causing less post-operative bleeding (50) as well as less inflammatory responses (51, 52). A meta-analysis from 2014 indicates that because of less blood loss, there is less use of blood products which may lead to impaired renal failure (53). They are also associated with less pain, lower infection risk and a better cosmetic result, due to the smaller incision (50). Economically the minimally invasive procedures produce lower costs and shorter hospital stays (54). Mini AVR being a cause for new onset atrial fibrillation remains a controversial topic (55), as well as association with longer aortic cross clamp and operation time (50). Due to these clinical advantages, and despite the required skill and learning curve of the cardiothoracic surgeon, mini-AVR is a safe and effective alternative to conventional AVR and will therefore be executed more frequently.

1.5. Cardio pulmonary exercise testing

Through CEPT the body's cardiac, pulmonary and metabolic response to exercise can be evaluated. Cardiac response is obtained by a 12- lead electrocardiogram, constantly measuring heart rate, ST distance and blood pressure. Further it also provides breath-by-breath gas exchange measurements of oxygen consumption (VO2), carbon dioxide output (VO2), minute ventilation (VE) and tidal volume (VT), giving an idea about pulmonary and cellular respiration function (10). By combining assessments of pulmonary gas exchange (ventilation and cellular respiration), cardiac function, vascular function (BP) and muscular function (work load), all of these organ systems can be screened at once, through this rather simple and noninvasive test. Making CEPT such a valuable tool to discover pathologies of the limiting organ system and abnormalities only seen during exercise (10).
Previous studies have shown the value of CEPT measurements, by predicting worse outcomes in patients that were in need of aortic valve replacement (56, 57). Thus, in patients recovering from mini-AVR surgery the changes in cardiac, pulmonary and muscular function assessed with exercise tests, could also have diagnostic as well as prognostic value (58).

The assessment tool that is considered the gold standard, is the maximal CPET. It is an important and popular prognostic tool, used by physicians to assess exercise capacity, limitations or give diagnostic insight of patients with heart failure or other cardiac pathologies (59, 60). The value that is used to evaluated exercise capacity is the maximal oxygen consumption and maximal HR. It is defined as the maximal amount of oxygen that can be taken up by the body, transported by the cardiovascular system and absorbed from the blood by the contracting muscles (10). Even though maximal CPET is the gold standard many patients with cardiac diseases should under no circumstances perform maximal exercise test, due to the high risk of complications. This also being the case for AS patients, were maximal exercise can lead to impaired MAP and sudden heart death. Maximal CPET is therefore not an adequate tool to assess patients suffering from AS. A safer and more suitable assessment for AS patients is submaximal CPET. It is a good indicator of cardiovascular and autonomic system function as well and even predict cardiac outcomes and death (61, 62). Compared to maximal CEPT, submaximal is characterized as being below the anaerobic threshold, which is the point during exercise were the muscles can no longer rely on aerobic glycolysis for ATP production alone but also need anaerobic glycolysis. Anaerobic glycolysis leads to accumulation of lactate and higher CO^2 production, therefore a submaximal exercise test can be defined as capillary lactate level under 4mmol/L or respiratory exchange ratio below 1.1. Heart rate, cardiac output and blood pressure stay on reasonably constant levels compared to maximal exercise. In fact, the lower the body can keep peak heart rate at moderate working rate the higher the fitness level (16). Since commencing exercise CO is increased by augmented SV, mediated through the Frank

Starling mechanism, only if the workload keeps progressing HR needs to increase CO even higher. Therefore, the later HR needs to rise, to increase CO, the better the systolic contractility and diastolic relaxation during exercise (63). After submaximal exercise faster heart rate recovery takes place because of less sympathetic activation (15).

During the evaluation of minimally invasive interventions, regularly only morbidity and mortality (‘hard endpoints’) are considered when evaluating procedure outcome. Functional measurements are seldom taken into consideration. After recovering from minimally AVR surgery these functional measurements (‘soft endpoints’) could be of high value, unmasking abnormal recovery, even before symptoms appear. This could then make earlier interventions possible and play a major role in improving follow-up of elderly patients after mini-AVR. It has been postulated in previous studies, that recovery after surgery in elderly patients is often slow and complicated (64). The reason being loss of function in many organ systems with aging. Surgical stress can lead to systemic inflammatory response, which is linked to worse outcome and contributes to complications during recovery in the days and weeks after surgery (65, 66). To get an insight perspective on postoperative recovery and prognosis after mini-AVR, these functional measurements (‘soft endpoints’) can be of high value (67, 68).

2. Aims and Objectives

Physiologic cardiovascular system function in rest and during exercise has been researched for decades (2, 3) and has been discussed in detail in the previous chapters. Further the pathologic effects of aortic stenosis on the cardiovascular and autonomic system are well investigated, these effects being autonomic imbalance (45), left ventricle hypertrophy (41) and dysfunction (42, 43).

In the literature there is no information to be found on how recovery becomes apparent in patients after minimal aortic valve replacement. Especially no insight was found on changes of cardiovascular parameters after minimal aortic valve replacement during early recovery. For this reason, further research needs to be done to identify how minimal aortic valve replacement interventions effect cardiovascular function parameters.

Cardiovascular parameters analyzed during early exercise testing following minimal aortic valve replacement, have not been assessed in such early recovery phases as in this study. *We firstly hypothesize that minimal aortic valve replacement will lead to better outcomes in heart rate profile in the recovery phase*. We are expecting the improvements to be arise in terms of *improved hemodynamic data*, *autonomic function* as well as recovery time and therefore quality of live. From these expected changes in cardiac and autonomic function, a better understanding of post-operative recovery, as well as possible worsening of the post-operative outcome could be deviated. Negative changes in hemodynamic and autonomic function could be linked to anomalous recovery of cardiac function. They could be detected earlier than usual and lead to faster and more effective interventions.

The following cardiovascular parameters were assessed in this study: Heart rate recovery is a sensitive marker for autonomic function. Reduced heart rate recovery is the incompetence of the body to lower heart rate efficiently after exercise. An abnormal heart rate recovery is an independent predictor of all- cause mortality and sudden death (19). It is further a parameter that is linked to autonomic imbalance, a low fitness form and overall mortality (8). It will be calculated from the difference between peak HR and HR two minutes into recovery phase. It will then be expressed as heart rate decrement, being a parameter for autonomic function. *We expect, after minimal aortic valve replacement intervention, an improvement of heart rate decrement and recovery as well a reduction in rest HR and peak HR*. In particular, for patients treated with β-blocker a post-operative decrease in rest and peak HR is assumed. These cardiovascular parameters will be compared at three times (pre-operative, 5 days post-operative and 3 weeks post-operative).

Studies show higher resting heart rate takes place in aortic stenosis patients. Higher resting heart rate is thus associated with greater aortic stenosis progression rate (44, 44). The *second objective of this study is therefore, comparing the investigated cardiovascular*

parameters (rest HR, peak HR, HR recovery and HR decrement) of patients with severe aortic stenosis pre-operatively to healthy age gender and BMI matched individuals. It is hypothesized that aortic stenosis patients score a higher rest HR pre-operative compared to the healthy control group. Further a lower rest HR for aortic stenosis patients' pre-operative, compared to post-operative is expected.

Aortic stenosis correlates highly with autonomic imbalance, this can be seen in a reduction in heart rate recovery and lower maximal heart rate in aortic stenosis patients (47). We therefore suppose that autonomic imbalance is present in the aortic stenosis sample group. Since lower HR recovery was proven to be a predictor of death and need for aortic valve replacement intervention (47), it could give an indication of patient outcome. Autonomic imbalance caused by aortic stenosis normalizes within one year after aortic valve replacement (48). Based on these findings *we hypothesize that aortic stenosis patients score a lower HR recovery and HR decrement than healthy controls.*

For safety reasons aortic stenosis patients were tested with submaximal exercise. Because an abnormal heart rate recovery is an independent predictor of all- cause mortality and sudden death (19), even if assessed with submaximal exercise (61).

3. Materials and Methods

3.1. Ethical approval

The institutional ethical board at Jessa Hospital and Hasselt University (Hasselt, Belgium) where the study was carried out, approved to the research protocol of this study. Also, all AS patients, as well as healthy individuals involved in the study signed informed consents after they were informed on the aim of the study.

3.2. Patient selection

This study was carried out in Jessa hospital, Hasselt Belgium, from August 2016 to December 2017. During that time 32 AS Patients, male and female, with severe AS and need for aortic valve replacement, as well as 32 healthy controls took part in this study. I was directly involved in collecting and analyzing the data of 10 AS patients, who were fully gender, age and BMI matched with 10 healthy individuals. I was able to take part in this prospective observational study, which focused mainly on oxygen uptake capacity parameters and involving 64 subjects overall. My assignment was, to analyze these 20 subjects (10 AS patients and 10 healthy control) in terms of cardiovascular parameters involving heart rate, heart rate recovery and heart rate decrement.

The 10 AS patients performed an SM-CPET one day prior to undergoing mini-AVR surgery, 5 days and 3 weeks after the surgery. The healthy control group performed only one SM-SPET under the same conditions as AS patients. All subjects in the control group were able to perform the SM-CPET. From the 10 AS patients all 10 complete the full protocol pre-operative and the 5^{th} post- operative day. After the AVR surgery 5 of 10 AS patients were treated with β-blocker medication for antiarrhythmic prophylaxis. The decision for the β-blocker treatment was made by the treating surgeon. β-blockers, are negatively chronotropic, inotropic, bathmotropic and dromotropic and therefore highly interfere with the objectiveness of heart rate and heart rate recovery measurements. Hence the AS group (n=10) was split into two equal groups. One group (n=5) with β-blocker therapy post-operative and one group without (n=5) β-blockers. Three weeks after surgery the SM-CPET was repeated and a drop out of one patients was observed. This patient could not attempt the SM-CPET because of rehospitalization due to complications.

The subjects participating were chosen through the following inclusion criteria: Severe Aortic stenosis (valve area ≤ 1.0 cm^2) requiring aortic valve replacement surgery for the first time. Also, the subjects were only allowed to participate in the study after approval from the treating cardiologist.

AS patients were excluded from the study if they were not able to perform an exercise test because of physical limitations, had either surgery for coronary artery or peripheral artery disease and or could not follow a standardized rehabilitation program.

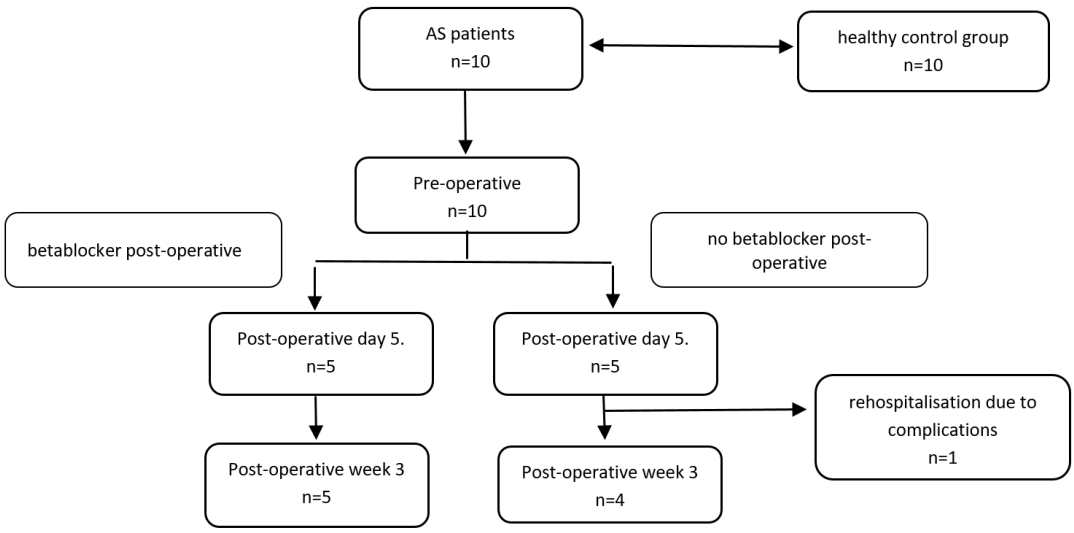

Figure 11. Flowchart of study population: AS patients were compared with a matched control group. After mini-AVR surgery they were split into two groups, depending on their beta blocker medication. Into no beta blocker post-op and beta blocker post-op group. In the no beta blocker group on patient dropped out, do to rehospitalization.

3.3. Study design

The study has a cross-sectional, prospective, observational design character. The entire study design is shown in Figure 12. The first measurements were taken preoperative one day before surgery. The second measurements were taken on day five post-operative through submaximal cardiopulmonary exercise test (SM-CPET). Then submaximal CPET was repeated 3 weeks after surgery, following a 3 months' rehabilitation program. To compare the pre-operative cardiovascular parameters of the AS patients with healthy individuals. A healthy age and gender matched control group was tested once, performing the same CPET exercise protocol as the Aortic stenosis group.

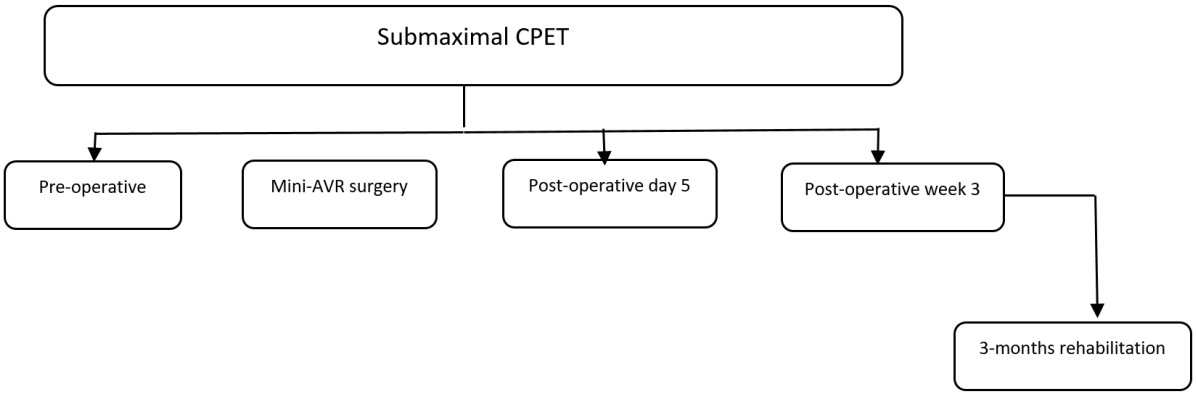

Figure 12. Shows study design CPET was performed at 3 time points: pre,-post-operative 5 days and 3 weeks followed by a 3 months rehabilitation.

During the submaximal CPET protocol, the following measurements were taken to research the cardiovascular response during exercise. These measurements include: Heart rate at rest (rest HR) defined as the average of the 3 minutes commencing submaximal CPET. Peak heart rate (SSHR) was defined as the average of the 2 minutes of peak exercise. Heart rate recovery (HRR) defined as the average of 2 minutes, 2 minutes into the recovery phase. To assess autonomic function changes, the difference between peak heart rate and heart rate recovery was defined as decrement of heart rate (DHR).

From all the measurements taken, I was directly involved in collecting and analyzing the data, of ten patients under the guidance of Professor Dr. Dominique Hansen.
For my part of the study pre-operative, early post-operative (5^{th} day) and three weeks' post-operative parameters are significant. Hence, I analyzed and compared the data and groups at these three points of time. Only the data from subjects that completed the full protocol was used for final statistics.

3.4. Measurements

The detailed cardiovascular parameters rest heart rate, peak heart, heart rate recovery, heart rate decrement and oxygen uptake (VO2), for other parts of the study, were constantly obtained through sub maximal cardiopulmonary exercise testing (CPET). The subjects had to perform the CPET on an electronically braked cycle ergometer (eBike Basic from General Electric GmbH Germany). The subjects, both AS patients and healthy controls, were instructed not to do any exercise the day before or on the day of the pre-operative exercise test. Furthermore, they had been advised only consume a light meal at least two hours prior to the test.

Subjects were seated on the bike for three minutes to obtain resting heart rate. Blood pressure were measured during rest using (Omron, HEM-7131-E, Omron healthcare Europe B.V., Netherlands).

Heart rate was measured for two minutes commencing exercise and averaged to get the get resting heart rate (rest HR). After that the subjects performed three exercise bouts of 6 minutes each, with 6 minutes of rest following every bout. Resulting in a total of 39 minutes of exercise. They were instructed to cycle 6 minutes at a rate of 70 rpm, against a resistance of 25% of predicted cycling power output. The predicted cycling power output was calculated using the equation.

Men: $25\%\ predicted\ cycling\ Wmax = \frac{(-1{,}78 * age) + (0{,}65 * weight) + (1{,}36 * lenght) - 45{,}4}{4}$

Women: $25\%\ predicted\ cycling\ Wmax = \frac{(-1{,}19 * age) + (0{,}96 * lenght) + 28{,}1}{4}$

Throughout the exercise testing, heart rate was continuously monitored by a 12- lead ECG device (Kiss, Anandic medical systems INC, Feuerthalen ZH, Switserland). For a different master thesis pulmonary gas exchange was measured continuously breath-by-breath with a mass spectrometer and volume turbine system (Jaeger Oxycon, Erich Jaeger GmbH, Germany).

During each six-minute exercise bout peak heart rate was measured. It was defined as the average heart rate during the last two 2 minutes of peak exercise during each bout. For final analysis all three bouts were averaged, for more valuable data.

Six minutes of cycling were followed by an additional six minutes of resting on the bike. During each six-minute recovery period a two minutes' window to measure heart rate recovery (HRR) was defined. The window being the average of 2 minutes, 2 minutes into the recovery phase. Heart rate decrement indicates autonomic system function and disbalances (14). It was calculated from peak heart rate during every bout and HR recovery during each six- minutes resting period. The difference between the two measurements, was calculated for every exercise bout and was defined as DHR.

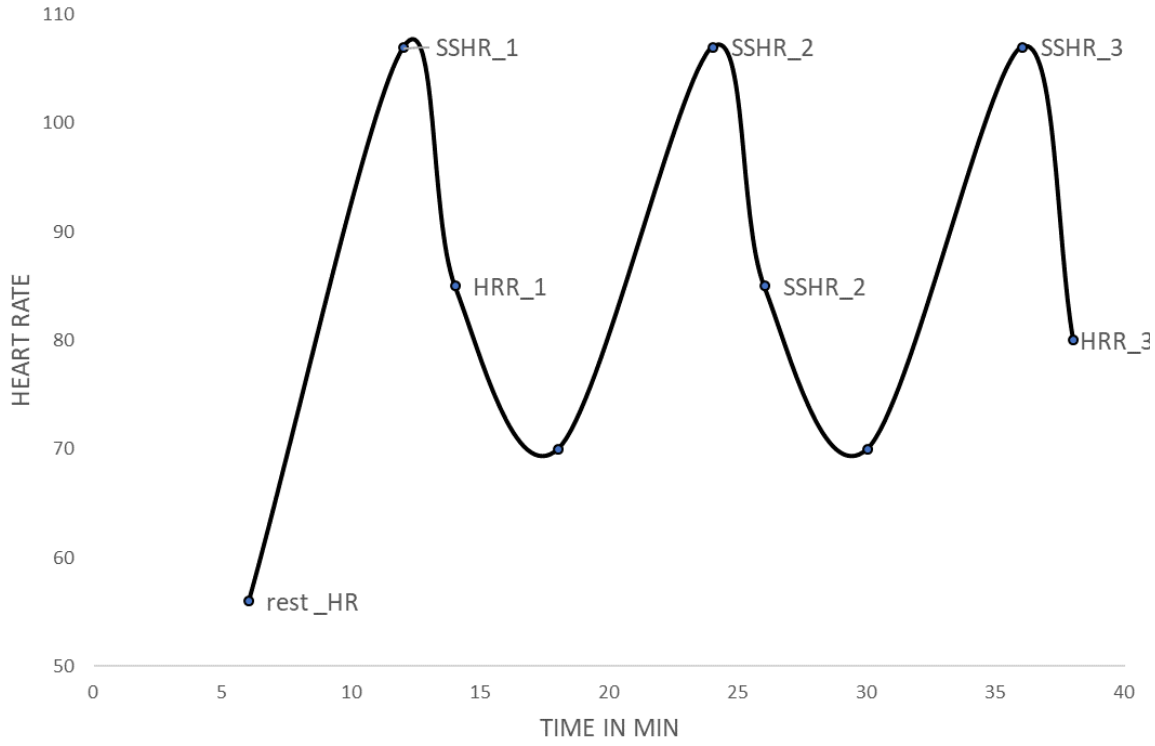

Figure 13. Shows the protocol of the CEPT with 3 bouts at 6 min. exercise and 6 min. recovery. The variables are measured during every bout and averaged for final analysis.

All variables, that were obtained during the three bouts, (SSHR, HRR, DHR) were then average, to get one number for final analysis. The overall twelve minutes, consisting of six minutes cycling and six-minute resting were repeated three times for a total of 36 minutes and are described in figure 13.

During the six minutes resting period on the bike, blood lactate concentration (mmol/l) was analyzed with a portable device (Accutrend Plus®, Roche Diagnostics Limited, Sussex, UK) by taking a capillary blood sample from the fingertip. Capillary blood lactate level was always under 4 mmol/l, therefore CPET can be assumed as submaximal. In addition, pulmonary gas exchange, oxygen uptake (VO2), (VCO2) and expiratory volume were assessed breath by breath for other parts of this study. These measurements obtained during rest as well as (VO2), (VCO2) were analyzed in a different master thesis and therefore had no consequences for my part of the study. However, from (VO2), (VCO2) the respiratory exchange ratio (RER) was calculated. It was kept under 1.1 to classify the exercise test as submaximal.

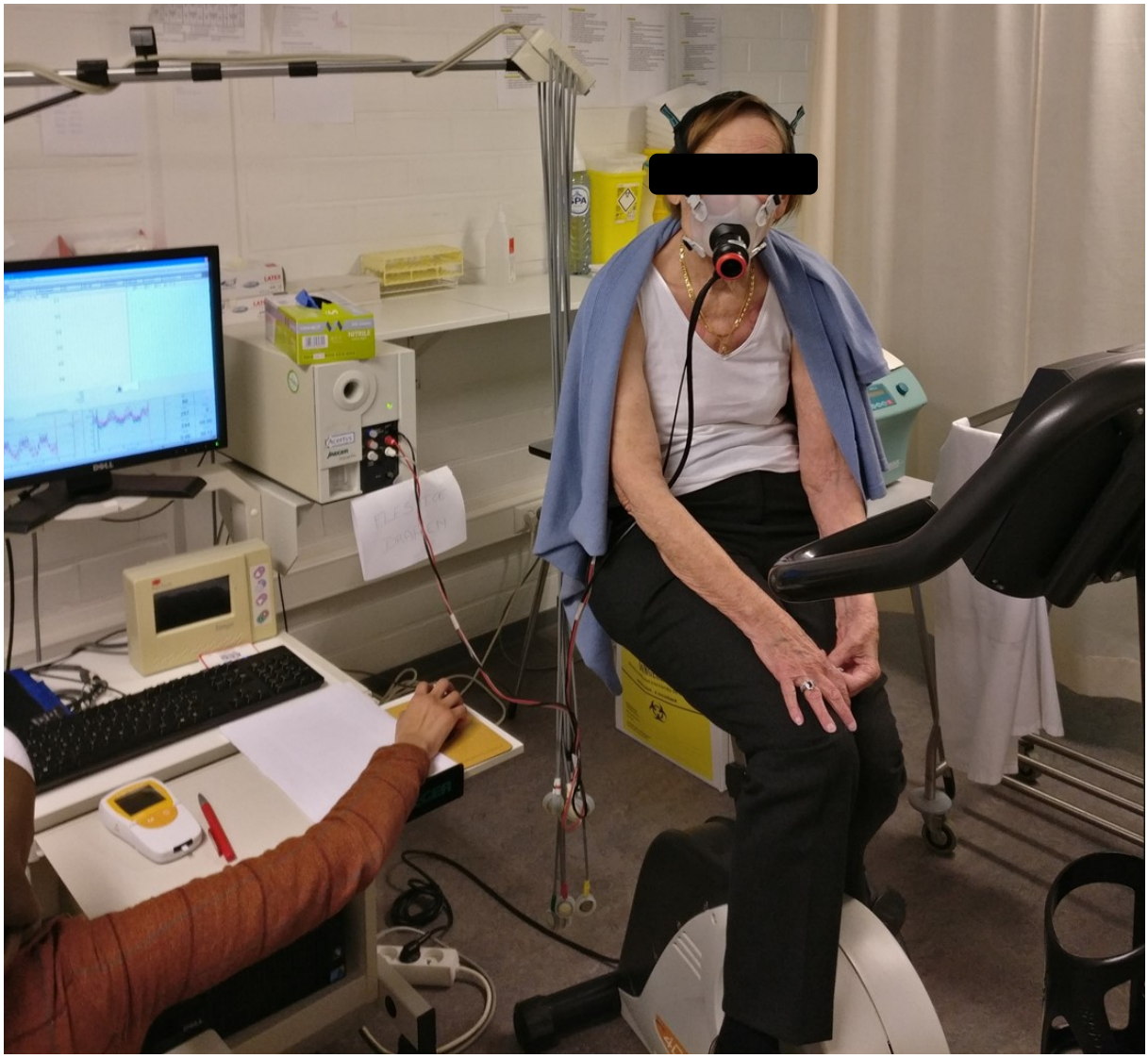

Figure 14. Shows AS patient after completing CPET protocol.

3.5. Minimally Invasive Aortic Valve replacement procedure

3.5.a. Anesthetic management

Prior to the procedure all Patients received standard premedication of Diazepam 10 mg one hour before arriving to the operating room. The anesthesia was performed with intravenous Sufentanyl and Propofol. Muscle relaxation was achieved with Pancuronium (0.1 mg/kg). To maintain the Anesthesia a combination of Propofol (2 – 3 mg/kg/h) and Isoflurane were given. A full dose of Heparin (300 IU/kg intravenously) was given to counter coagulation and activated clotting time was keep above 400 seconds. After completing the procedure heparin was reversed with protamine at 1:1 equivalent dosage.

3.5.b. Cardiopulmonary bypass

For Cardiopulmonary bypass the Maquet HL30 heart lung machines (Maquet Cardiopulmonary, Hirrlingen, Germany) was used. It uses minimal extracorporeal circulation (MECC) which compounds of a totally closed Bioline heparin coated system circuit with rotaflow centrifugal pump, Quadrox-i microporeus membrane oxygenator and venous bubble trap (VBT) (Maquet Cardiopulmonary, Hirrlingen, Germany). Also, a blood collection reservoir connected to the VBT was integrated in the circuit but no open venous reservoir is present. Autologous retrograde priming of the MECC was performed, reducing priming volume to 250 cm. Intrapericardially bloodshed was drained via a cell saver drainage. A pulmonary artery vent (Medtronic Inc, DLP catheter 13 Fr, Minneapolis, USA) was inserted via the main pulmonary trunk distal to the pulmonary valve. Then the pulmonary artery vent was directly connected to the venous bubble trap maintaining the same level of vacuum suction. Aortic root vent ran via a drip chamber and was then connected to the venous bubble trap. Continuous carbon dioxide (CO 2) field flooding (6 l/min) was maintained during the entire procedure. Antegrade warm blood cardioplegia (Calafi ore, 1.7 mmol/ml potassium) was administered via the aortic root and repeated every 15 – 20 minutes then selectively via the coronary ostia. Nasopharyngeal temperature is kept at 34° C.

3.5.c. Surgical procedure

Minimal invasive replacement of the aortic valve was performed by Dr. Alaaddin Yilmaz using minimal extracorporeal circulation. The patient was in supine position with access to the groin for arterial and venous femoral cannulation. A 4 – 5cm median, sub-jugular skin incision was carried out in the upper sternal region. Followed by a J-shaped partial sternotomy into the right third intercostal space, which was done with an oscillating saw. An appropriate sized femoral artery cannula (Medtronic Inc.) was inserted using Seldinger technique. This is followed by insertion of a dual stage venous 21 to 25 french cannula (Medtronic Inc.) under transoesophageal echocardiography (TEE). The aortic valve procedure was performed in a standard fashion. After the aortic valve procedure is completed, the venous suction is discontinued temporarily and air is evacuated from the heart using TEE guidance. Temporary pacing wires and chest tubes are placed. After completing the procedure five patients received bisoprolol individually dosed, to prevent cardiac arrhythmia. The individual indication for beta blockade treatment was made by the treating surgeon.

4. Results

4.1. Study population

In this prospective observational study, 10 patients with severe AS who received a new aortic valve via mini-AVR surgery, were fully age-, gender- and BMI matched with 10 healthy controls free of any chronic diseases. Subject baseline characteristics and descriptive data are summarized in table 1.

Table 1. Descriptive data and characteristics of healthy controls and AS patients.

Variable	Healthy controls	AS patients
Subjects (n)	10	10
Male	5	5
Female	5	5
Age (years)	63.7 ± 12.7	63.3 ± 12.02
Body Mass Index (kg/m^2)	25,7 ± 3,4	26.4 ± 4.1
Medication		
β-blockers	0	5

Values are represented as mean±SD.

For final statistical analysis the data of 20 subjects was analyzed with SPSS. Four depending variables were included into final analysis. Rest HR was defined as the average of the 3 minutes commencing SM-CPET. SSHR was defined as the average of the 2 minutes of peak exercise. HRR was defined as the average of 2 minutes, 2 minutes into the recovery phase and DHR was defined as the difference between maximal heart rate and heart rate recovery. SSHR, HRR and DHR variables were measured during all three exercise bouts and then averaged to create one number. That leaves one number per variable per time point: Time point 1 (pre-operative), time point 2 (post-operative 5 days), time point 3 (post-operative 3 weeks). Overall 4 variables at three-time points for every patient (Rest_HR_1-3), (SSHR_1-3), (HRR_1-3), (DHR_1-3). AS patient number 5 out of the no β-blocker group could not attempt the SM-CPET 3 weeks' post-operative. Therefore, an approach for missing data was done by using the data from the second-time point (5th day post-operative) fill in for the third-time point.

4.2. Test for normal distribution

All depending variables were tested for normal distribution with Shapiro- Wilk and Kolmogorov- Smirnov. The statistical value for normal distribution after Shapiro- Wilk are presented in table 2.

Table 2. Showing results of Shapiro-Wilk test of normality.

Variable	Statistic	df	p-value
BMI_1	.958	9	.775
Rest_HR_1 (bpm)	.910	9	.319
SSHR_1 (bpm)	.942	9	.599
HRR_1 (bpm)	.951	9	.703
DHR_1	.960	9	.799
BMI_2	.956	9	.754
Rest_HR_2 (bpm)	.945	9	.634
SSHR_2 (bpm)	.938	9	.565
HRR_2 (bpm)	.975	9	.934
DHR_2	.792	9	**.017**
BMI_3	.924	9	.426
Rest_HR_3 (bpm)	.927	9	.453
SSHR_3 (bpm)	.921	9	.401
HRR_3 (bpm)	.913	9	.340
DHR_3	.973	9	.919

For fat marked results are statistically significant.

Significant difference was defined as p-value below 0.05. No significant difference was show (p>0.05) for 11 of 12 variables. Sig. difference was seen in DHR_2 *p=0.017* (heart rate decrement at 5 days post-operative). This finding was ignored for further analysis. Therefore, normal distribution can be assumed. The requirement for further statistical analysis with t-test is thus given with the normal distribution of the data.

4.3. Submaximal cardiopulmonary exercise test parameters of healthy controls versus AS patients

An independent-samples t-test was conducted to compare AS patient group pre-operative (first-time point) and control group. The four variables Rest_HR. SSHR, HRR and DHR were independently compared and a p-value below 0.05 was defined as statistically significant. There was a slightly not sig. difference between rest HR in the AS group *M*= 67.6*, SD*= 9.8 and the healthy control group *M*=76.3*, SD*= 12.5 *conditions; t(18)=-2.29, p=.064.* No significant difference was found for the variables SSHR, DHR and HRR as shown in the table blow.

Table 3. Depending variables healthy controls vs. AS patients' pre-operative.

Variable	Healthy controls	AS patients	p-value
Rest_HR (beats/min)	67.6 ± 9.8	76.3 ± 12.5	0.064
SSHR (beats/min)	89.9 ± 9.1	91.5 ± 7.2	0.646
HRR (beats/min)	83.3 ± 5.9	79.1 ± 9.9	0.266
DHR (SSHR-HRR)	6.6 ± 5.8	10.26 ± 4.4	0.089

4.4. Submaximal cardiopulmonary exercise test parameters pre-operative vs. 5 days' post-operative vs. 3 weeks' post-operative

The four variables in AS group were then further analyzed, by comparing the three-time points using two-way ANOVA. The three-time points were classified as within subject factor. The difference in β-blocker medication, separating the AS group into two groups, was expressed as between subject factor.
For each variable one ANOVA was calculated. The results are presented in table 4.

The requirement for a two-way ANOVA, was checked by using Levene test for homogeneity of variances. No sig. difference was found $p>0.05$ for every variable, indicating equality of variances.

Table 4. Two- way ANOVA with 3 within subject factors (time points) and 2 between subject factors (β-blocker medication).

		Time 1	Time 2	Time 3	Sig. of within subject	Sig. of between subject
variable	**medication**	**Mean±SD**	**Mean±SD**	**Mean±SD**	**p-value**	**p-value**
Rest_HR	No β-blocker	74.0 ± 7.6	78.2 ± 10.5	61.3 ± 9.69	***.025***	.252
	β-blocker post-op	74.5 ± 15.2	75.2 ± 4.9	74.4 ± 15.9	.108	
SSHR	No β-blockers	92.3 ± 3.9	90.1 ± 10.4	75.0 ± 9.0	**.002**	*.089*
	β-blocker post-op	90.9 ± 10.0	97.8 ± 12.4	84.4 ± 12.8		
HRR	No β-blocker	79.6 ± 7.1	82.0 ± 11.1	64.3 ± 10.7	**.011**	.334
	β-blocker post-op	78.5 ± 13.1	81.4 ± 8.2	73.8 ± 12.7		
DHR	No β-blocker	12.7 ± 7.1	8.1 ± 2.9	10.6 ± 4.5	.747	.248
	β-blocker post-op	12.3 ± 4.9	16.4 ± 9.7	10.5 ± 4.0		

Fat marked results are statistically significant. Italic marked results were slightly not sig. Time 1 = pre-operative; time 2 = post-operative 5 days; time 3 = post-operative 3 weeks.

4.4.a. Results peak heart rate

There was a sig. main effect found between the within subject effects (time) for peak heart rate (SSHR) *F(2, 24) = 7.758, p=.002*. No significant difference was found for the between subject effects *F(1, 24) = 3.126, p=.089*. The interaction was further not significant *F(2, 24) = 1,36, p=.275.*

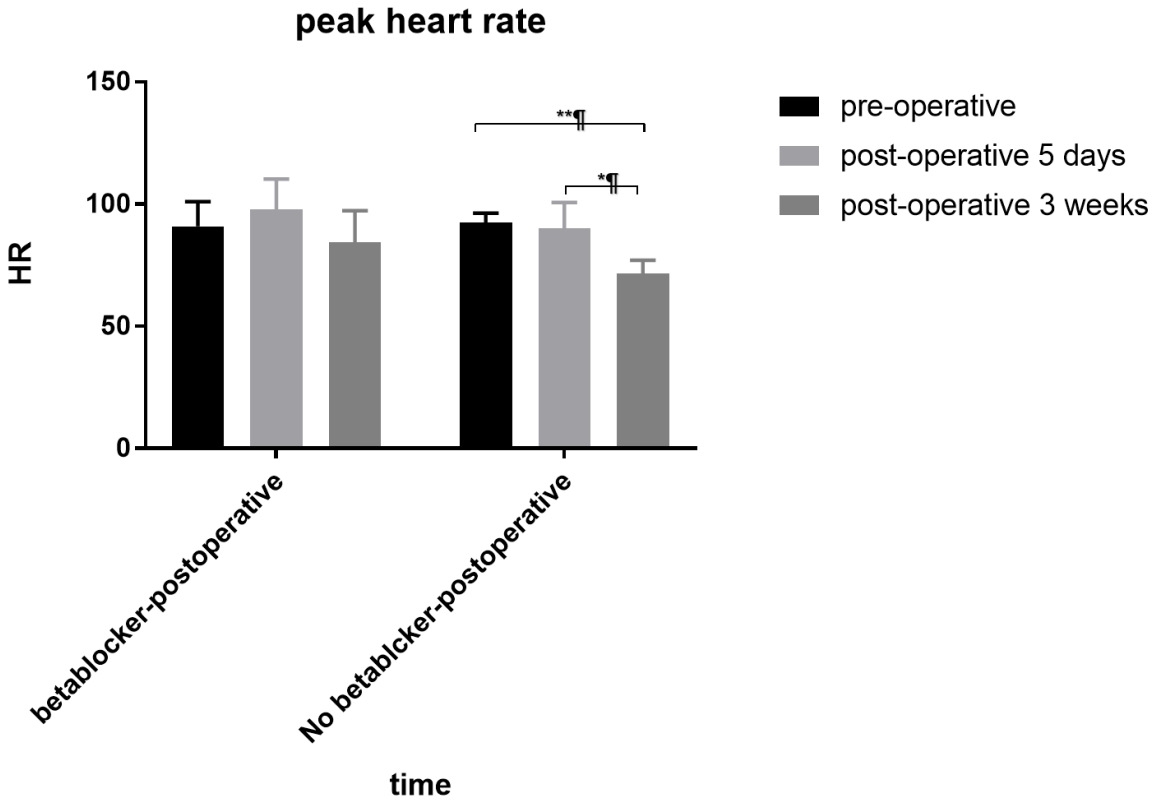

*Figure 15. Shows sig. difference peak heart rate *p=.0187 between time point 2 and 3. ** p=.0079 between time point 1 and 3 in no β-blocker group.*

Bonferroni post-hoc test for multiple comparison was calculated, in order to clarify between which time-points the sig. differences lays. For the within subject effects that are sig., alpha levels of *.05* were defined.

Results, shown in figure 15, indicated that SSHR, in the no β-blocker group, was significantly lower at time point 3 (post-operative 3 weeks) *(M= 71.58, SD= 5.49)* than those at time point 2 (post-operative 5 days) *(M=91.18, SD= 10.45), p=.0187* and to time point one (pre-operative) *(M= 92.39, SD= 3.94) p=.0079.* The pairwise comparison between time point one *(M= 92.39, SD= 3.94)* and two *(M=91.18, SD= 10.45)* was statistically non-significant *p>.05*.

In the β-blocker group there was statistically no significance found for multiple comparisons, between time point one *(M= 90.93, SD= 10.08)* and time point two *(M= 97.80, SD= 12.48), p=.83* and time point three *(M= 84.42, SD= 12.83), p=.91.* Further no statistical significance was found between time point two *(M= 97.80, SD= 12.48)* and three *(M= 84.42, SD= 12.83), p=.12.*

4.4.b. Results heart rate recovery

For the variable heart rate recovery (HRR) statistically sig. main effect was found between the within subject effects (time) in both groups *F (2, 24) = 5.407, p=.011*. Ns. difference concerning the between subject effects *F (1, 24) = .9707, p=.33.* Also, the interaction was not significant *F (2, 24) = 1.478, p=.24.*

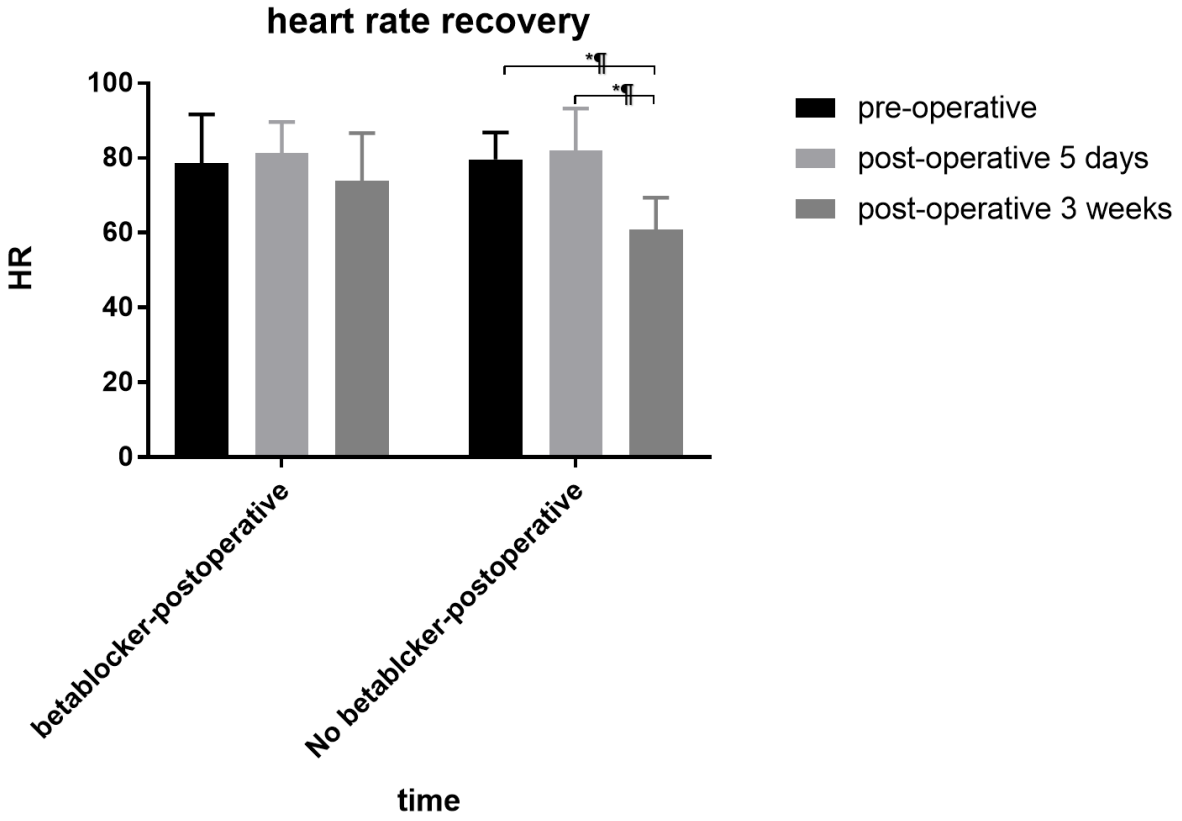

*Figure 16. Shows heart rate recovery sig. differences between time point 3 and 2 *p=.011 and between time point 1 and 3 *p=.026 in the no β-blocker group.*

Bonferroni post-hoc test for multiple comparison indicated that HRR, in the no β-blocker group, was significantly lower at time point 3 (post-operative 3 weeks) *(M= 60.85, SD= 8.48)* than those at time point 2 (post-operative 5 days) *(M=82.06, SD= 11.17), p=.011* and at time point one (pre-operative) *(M= 79.63, SD= 7.17) p=.026.* The pairwise comparisons between time point one *(M= 79.63, SD= 7.17)* and two *(M=82.06, SD= 11.17)* was statistically non-significant *p>.05*.

For the β-blocker group no statistical significance for multiple comparisons was found, between time point one *(M= 78.55, SD= 13.10)* and time point two *(M= 81.40, SD= 8.26), p>.05* and time point three *(M= 73.84, SD= 12.75), p>.05.* Further no statistically significance between time point two *(M= 81.40, SD= 8.26)* and three *(M= 73.84, SD= 12.75), p>.05.*

4.4.c. Results rest heart rate

For the variable rest heart rate (rest_HR) slightly no statistical difference was found between the within subject effects *F (2, 24) = 2.443, p=.108*. No statistical difference concerning the between subject effects *F (1, 24) = 1,31, p= .263* was found, meaning no difference between the groups can be assumed.

However, Bonferroni post-hoc test for multiple comparison showed a statistically significant difference in the no β-blocker group between time point 2 (post-operative 5 days) *(M= 78.21, SD= 10.57)* and time point 3 (post-operative 3 weeks) *(M= 58.11, SD= 7.45),* p=.025. No statistical significant difference was found in the β-blocker group between the three-time points.

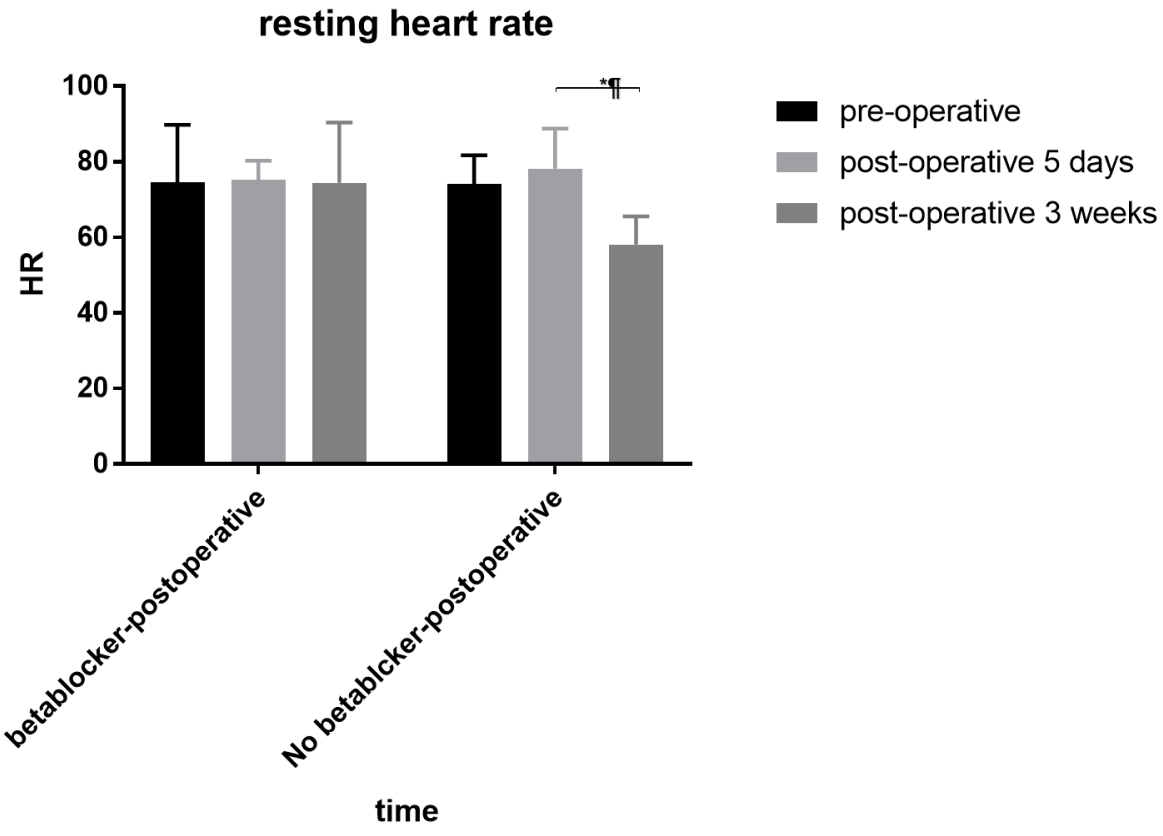

*Figure 17. Shows resting heart rate with sig. difference between time point 2 and 3 **

4.4.d. Results heart rate decrement

For the variable DHR no statistically significant difference was found between the within subject effects (time) *F (2, 24) = 0.2942, p= .747*. Also, ns. difference concerning the between subject effects *F (1, 24) = 1,399, p=.248.* And further no statistical sig. difference for the interaction between the groups *F (2, 24) = 1,69, p=.205.* However, the mean values indicated a lower trend 3 weeks post-operative *(M= 10.65, SD= 4.67)* compared to pre-operative *(M= 12.57, SD= 6.01)* in both groups. In the no beta blocker group at 5 days post-operative DHR with a lower mean value *(M= 8.12, SD= 2.98*) than pre-operative *(M= 12.75, SD= 7.10*). In the β-blocker group however, an increase in DHR mean value at 5 days post-operative *(M= 16.40, SD= 9.71*) over pre-operative *(M= 12.39, SD= 4.92*) values was found.

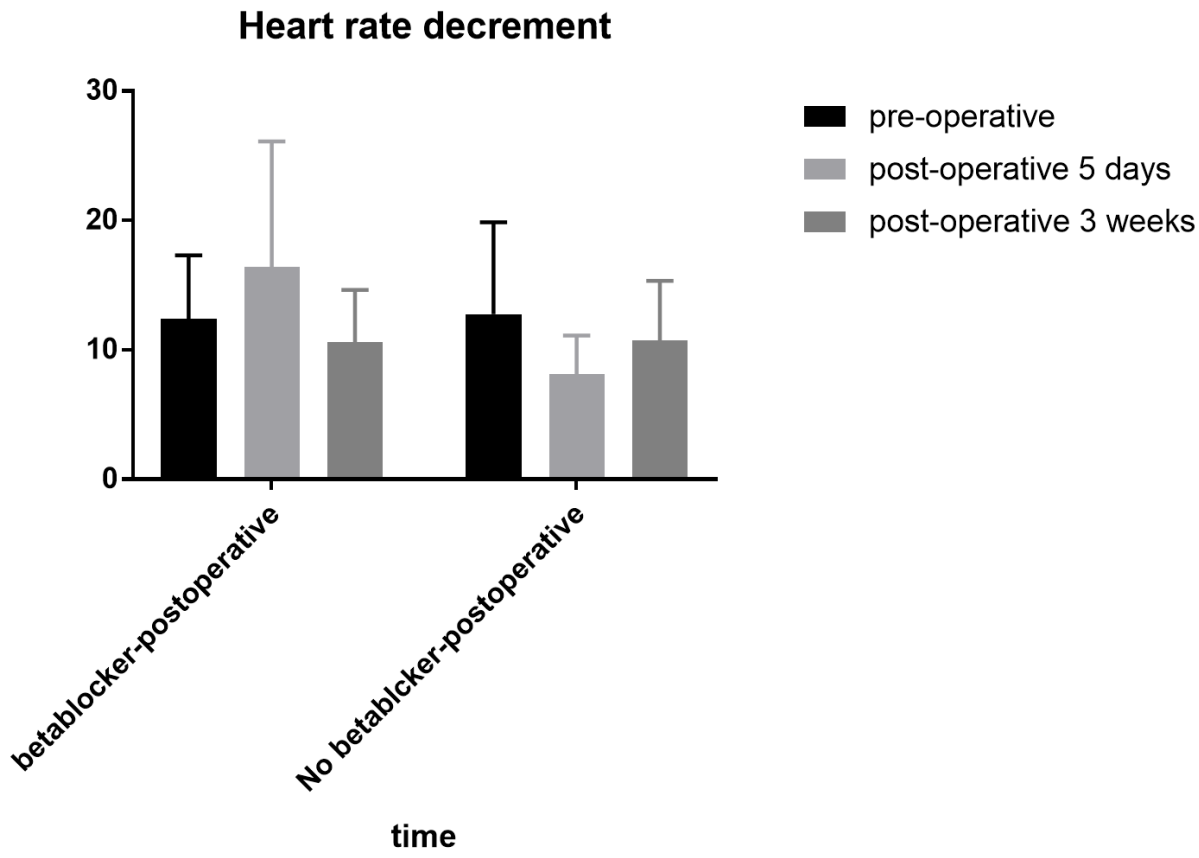

Figure 18. Shows heart rate decrement at the three-time points, in β-blocker and no β-blocker group without sig. difference between the time points.

5. Discussion

In this present prospective observational study, the impact of mini-AVR surgery on cardiovascular system function parameters, measured by heart rate profile, before, during and after exercise were investigated to show the effect of this relatively new surgical approach. The negative effects of AS on cardiovascular and autonomic system function have been researched in the past decades and is therefore well known (1, 5, 37, 41, 42, 44, 45, 47). Further known is that maximal exercise tests, even though being the gold standard tool to assess CVS function, is very dangerous for patients suffering from AS. Submaximal exercise testing is the much safer choice, plus it has been proven to be too a good indicator for CVS function and prognosis (61). However, cardiovascular system parameters have never been assessed at an earlier stage following mini-AVR surgery than in this study. We therefore expected to get a new insight of early cardiovascular system reaction and recovery after these interventions. This could have enormous prognostic value as well as give a better understanding of how early recovery becomes apparent. The evaluation of the subjects started already on the 5th post-operative day and was repeated 3 weeks into the recovery phase.

The results indicated that 5 days after surgery no improvement of CVS and autonomic function have accrued, since no statistical significant difference was found for all variables of the heart rate profile. However, 3 weeks after AVR surgery an improvement of the heart rate profile indicates an improvement of cardiac function, even though no accelerated in heart rate recovery and decrement was found. Suggesting that autonomic function does not improve 3 weeks after surgery but may take a longer time. Further no significant difference in the heart rate profile between the β-blocker group and the not β-blocker group was found. Cardiovascular and autonomic function was assessed in AS patients by using a submaximal exercise test, since studies have shown submaximal CPET is a good way to measure CVS and autonomic function (61).

Between the AS patients' pre-operative and healthy matched control group, for rest HR the results were found to be slightly non-significant. Even though resting HR mean values were higher in the AS patients compared to healthy individuals. The assumed higher rest HR in AS patients, expressing reduced cardiovascular autonomic function, is still expected. Possibly due to the relatively small sample (n=20) this effect could not be proven in this study. As a study indicates, smaller effects between groups can be not significant due to small sample size (69). Also, no statistical significant difference was found between the groups, for the variables peak heart rate, heart recovery and decrement. The difference between healthy individuals and AS patients is still assumed for these variables, due to the various negative effects of AS on CVS function. This effect however could, due to the small sample size, not be proven (69) in this present study.

5.1. 5 days' post-operative

At the second time point of the submaximal CPET (5 days' post-operative) no statistical significant difference was found for resting heart rate in both groups. This indicates that CVS and autonomic function, especially vagal tone since it is more active in rest, do not change 5 days after surgery. This is in line with a study indicating that autonomic dysfunction in AS patients recovers within one year after AVR surgery (48).

Furthermore, it is interesting that the expected lower resting heart rate in the β-blockaded group also did not accrue, since there was no significant difference between the two groups. This paradoxically not appearing difference, will be discussed below.

Peak heart rate at 5 days' post-operative showed no significant difference to pre-operative, indicating that there is no improvement of cardiac and CVS function within the first couple of days during recovery. A lower peak heart rate in submaximal exercise, suggesting a better cardiac function, could not be observed at 5 days' post-operative in this present study. These findings indicate that left ventricle function recovery after 5 days' post-operative did not accrue. This is in line with studies indicating that left ventricle function recovery expressed as a rise in LVEF and diastolic filling, needs about 30 days after AVR to recover (70). Left ventricle mass regression even takes up to 24 month in patients relieved from AS (71).

The expected acceleration in heart rate recovery post-operative 5 days could not be observed in this study. Since heart rate recovery is a marker for autonomic system function, it can be assumed that within 5 days of recovery from AVR no change in autonomic function accrued. Especially vagal tone plays the more important role in HR decrease, thus no change in parasympathetic system activity took place.

The expected improvement of autonomic function after mini-AVR surgery, expressed via heart rate decrement increase was not observed 5 days' post-operative. There was no significant difference between time point one (pre-operative) and two (5 days post-operative) for HR decrement indicating that autonomic function does not improve within the first days after AVR. Vukasovic, Florenzano et al. found that autonomic imbalance caused by AS, normalizes within one year after AVR (48). It is therefore assumed that also in this present study autonomic function needs longer to improve than 5 days.

Between the beta blockaded group and patients who did not receive beta blockers post-operative no significant difference was observed, neither in rest HR, peak, recovery or heart rate decrement. A possible explanation could be that the negative chronotropic effect of bisoprolol takes more time to lower heart rate significantly, about 2 weeks as Yamashita, Inoue et al. indicate (72).

Further the indication for bisoprolol post-operative was in this study, post-operative prophylactic antiarrhythmic effect, not frequency control. No titration of β-blockers was therefore done. This could lead to an underdosage of the β-blocker and not result in

significantly lower rest and peak heart rate. This assumptions are in line with a study from 2009 finding that by not titrating beta blockers, only 5,3% of the patients achieved their targeted heart rate (73).
Also, the beta blocker ingestion time could influence the negative chronotropic effects. Thus exercise tests should always be at the same time after beta blocker intake, because heart rate, especially maximal, depends on the time passed after β-blocker ingestion (74). The submaximal CPET could not always be performed at the ideal time, because of logistically reasons. This might also be leading to corruption on heart rate profile in the beta blocker group.

5.2. 3 weeks' post-operative

Three weeks after mini-AVR surgery significant lower rest HR in the non β-blockader group was observed compared to 5 weeks' post-operative and pre-operative. These findings suggest, as expected, an improvement of cardiac function after 3 weeks into recovery phase. The lower resting heart rate, as an indicator of cardiac function recovery, can be assumed since it seems the heart can, without the stenosis, eject a higher stroke volume with every contraction. Thus, produce the same CO as pre-operative, only at a lower resting heart rate. Further it has been proven that higher resting heart rate is not only associated with worse prognosis in AS patients (44) but also with cardio vascular mortality (75).
The reverse conclusion can be drawn in the group treated with bisoprolol after surgery. Since lower resting heart rate could not be found 3 weeks after surgery. These findings indicate that in this group a worse prognosis could be assumed and slower recovery of CVS function. The not observed negative chronotropic effect in these subjects, possibly caused by no titration and/or ingestion time differences, has been discussed in detail above.
Further results suggest that 3 weeks post AVR a reduction in peak heart rate expresses improvement in left ventricle and therefore CVS function. 3 weeks' post-operative the heart achieves, because of obstruction removal, a higher stroke volume and better contractility. Thus, heart rate under submaximal CPET does not need to rise as high to eject the needed CO. It is arguable that the not observed difference between the two groups in peak heart rate is again do to no titration and/or ingestion time differences, as exemplified earlier.
A significant lower HR recovery two minutes into recovery phase after 3 weeks compared to 5 days and pre-operative was found in both groups. However, since peak heart rate was equally lower, the HR decrement needs to be considered. For the variable heart rate decrement (DHR) no significant difference between repeated measures in both groups was found. Given the fact that DHR is a measure of autonomic function, in detail vagal activity, it does not show the expected improvement after the mini-AVR intervention. Therefore, this indicates that no improvement of parasympathetic activity 3 weeks after surgery has accrued. This leads to the postulation that autonomic function needs longer than 3 weeks to

recovery and supports Vukasovic, Florenzano et al., who investigated heart rate variability after AVR surgery. They came to the conclusion that autonomic dysfunction function caused by AS normalizes within one year after AVR surgery(48). We suggest that after a cardiac exercise rehabilitation program from 3-6 month an increase in autonomic function can be expected.

This assumption is supported by various studies indicating that an improvement in autonomic system function can already be seen after moderate exercise rehabilitation programs in healthy individuals (35) as well as patients with cardiac diseases (76). A study assessing autonomic function by using heart rate variabilities found, acceleration of parasympathetic activity takes place within 7 days during a 6 weeks training program (36). However, Piotrowicz, Baranowski et al. found no normalization in autonomic function after completing an 8 week exercise rehabilitation program (77). This indicates that an exercise rehabilitation program should at least last 3 months before reevaluation is considered.

5.3. Future perspective

In this present study the assumed increased autonomic function in AS patients could not be proven, probably caused by to small sample size. The negative effect of AS on autonomic system function is supported by the literature (45) and therefore its presents is still assumed in the participating AS patients. Thus, the evaluation of autonomic function at a later time, ideally after completing an exercise rehabilitation program, should be considered in the future. As discussed earlier a duration of at least 3 months' rehabilitation should be considered.

5.4. Limitations of this study

Nowadays it is postulated by many researchers, that the most valuable and popular method to assess autonomic function, in particular during submaximal exercise testing, is the analysis of heart rate variability (78). It is calculated by the duration of RR intervals. These intervals are not constant but continually fluctuate around the mean value. These fluctuations are mediated by complex neuronal mechanisms, are regulated by sympathetic and parasympathetic interaction and thus can detect much smaller changes in autonomic function. It is debatable that in this study heart variabilities should have been evaluated and could have given a more sensitive result of autonomic function than heart rate decrement or recovery. However, in this study it was not possible to calculated heart rate variability, because the heart rate could due to technical limitation not be measured beta by beta but only every 10 seconds. It remains controversial that in this present study further CVS parameter such as blood pressure and SV should have been analyzed. Since MAP in rest and SV during exercise are the relevant values that heart rate is regulated after. Hence, they

could have given a more detailed insight of CVS and autonomic function during recovery from mini-AVR.

Even though it has been proven that heart rate recovery after submaximal exercise testing has great value in assessing hard endo-points such as mortality (61), for evaluating functional capacities of CVS and autonomic function (softer endo-points) maximal exercise testing remains the more sensitive marker and therefore has more prognostic value.

Post-operative 5 out of 10 subjects received β-blocker medication with bisoprolol to prevent cardiac arrhythmia. Since bisoprolol is a cardio selective β-blocker it connects to β1 adrenergic receptors on the heart, preventing adrenalin to connect. This leads to negative inotropic and chronotropic reactions and could translate into a reduction in diagnostic accuracy. Peak HR, resting HR and systolic blood pressure likely would be reduced (63). Therefore, in this present study β-blocker intake should have been an exclusion criteria. However, since the sample size of the study population was already very small, it was not possible to exclude 50% of the participants. It would have been necessary though, to record the time of ingestion and the dosage of these medications before exercise testing, because of the effects described above. But since the main part of the study focused on oxygen capacity this data was not collected in the protocol.

In general, it can be presumed that the sample size of n=20 subjects was too small to show significant difference between AS and healthy control group. With a bigger sample size, even small significant differences can be proven (69) and in this case, might have shown more clearly the negative effects of AS on CVS function.

6. Conclusion

This present study indicates, that in early stages of recovery from minimally invasive aortic valve replacement no improvement of cardiovascular and autonomic system function took place in this sample, since no changes of rest, peak or heart rate recovery was observed 5 days' post-operative. 3 weeks post-operative lower resting and peak heart rates were observed, suggesting an improvement of cardiac function. However, no increase of heart rate recovery was found 3 weeks' post-operative, indicating that improvement of autonomic function takes longer than 3 weeks. Further no difference between the HR profile of AVR patients treated with β-blockers post-operative compared to AVR patients not treated with β-blocker was found. This leads us to the conclusion, that the chronotropic effect of β-blocker has a longer activation time than 3 weeks and might take titration. A difference between the heart rate profile of AS patients and a healthy matched control group could in this study not be shown, possibly due to small sample size.

In conclusion these findings indicate that AS patients do not profit within the first days after minimal AVR surgery but CVS function improvement can be seen after 3 weeks into the recovery phase.

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