DISSERTATION

PULSATILE HEMODYNAMICS AND EXERCISE CAPACITY-FOCUS ON HEART FAILURE WITH PRESERVED EJECTION FRACTION

submitted by

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for the Academic Degree of

Doctor of Medical Science

(Dr. scient. med.)

at the

Medical University of Graz

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2018

STATUTORY DECLARATION

“ I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz“.

DISCLOSURES

Part of this thesis has been published in Broufa M, Wassertheurer S, Hametner B, Zweiker R, Binder RK, Weber T. Pulsatile Hemodynamics Are Associated With Exercise Capacity in Patients With Exertional Dyspnea and Preserved Left Ventricular Ejection Fraction. Am J Hypertens. 2018 Apr 13;31(5):574–81. (1)

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Graz on the 5.06.2018

Maria Broufa

ACKNOWLEDGEMENTS

This is an author produced version of an article accepted for publication in the American Journal of Hypertension following peer review. The version of record (1) is available online at**:** http://www.ncbi.nlm.nih.gov/pubmed/29324983 doi: 10.1093/ajh/hpy001

I wish to express my sincere gratitude to Priv. Doz. Weber for giving me the opportunity to be part of his research team regarding HFpEF and to Prof. Dr. Zweiker for supporting me in completing the thesis at the medical university of Graz. I want to thank all supervisors for their support, guidance and encouradgement throughout the project.

I am greatfull to the contribution work of all article co authors: Ronald K. Binder[1], Bernhard Hametner[2],Siegfried Wassertheurer[2] Thomas Weber[1], Robert Zweiker[3].

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ABBREVIATIONS AND DEFINITIONS

A cm/s

Represents the late diastolic mitral flow velocity. If ventricular relaxation is impaired A velocity increases as there is a compensatory greater atrial contraction. Normal values are 0.4-0.8 m/s.

ACCF - American college of cardiology foundation

ACE – Angiotensin converting enzyme

AHA - American heart association

AIx % - Augmentation index

Augmentation index = AP/PP. It is the share of the augmentation pressure to the pulse pressure. It is a measurement of wave reflections.

AIx75 %

This represents the augmentation index normalized for a heart rate of 75 beats per minute for better comparability.

AP mmHg - Augmentation pressure

Augmentation pressure is the part of the central systolic blood pressure which can be explained by the influence of wave reflections on the central aortic waveform.

ARBs - Angiotensin receptor blockers

BMI kg/m^2 - Body mass index

The BMI is defined as the body mass divided by the square of the body height expressed in units of kg/m^2.

BR - Breathing reserve

BSA m^2 - Body surface area

Body surface area. Calculated via the Mosteller equation: BSA (m^2) = square root of (height (cm) × weight (kg)/3600).

CAD – Coronary artery disease

cGMP - Cyclic guanosine monophosphate

CHF – Chronic heart failure

CPAP - Continous positiv airway pressure

CRP – C reactive protein

CSA - Central sleep apnea

DBP mmHg - Diastolic blood pressure

aoDBP mmHg - Aortal diastolic blood pressure

Diastolic blood pressure measured at the ascending aorta.

bDBP mmHg

Diastolic blood pressure measured at the brachial artery.

cDBP mmHG

Diastolic blood pressure at the aorta derived non invasively.

DBP at rest mmHg

Diastolic blood pressure before the exercise testing.

DBP max mmHg

Highest diastolic blood pressure reached during exercise.

DD - Diastolic dysfunction

DHF – Diastolic heart failure

DPP-4 – Dipeptidyl peptidase 4

E cm/s

Represents the early diastolic mitral flow velocity. If ventricular relaxation is impaired E velocity decreases. Normal values are 0.6-1.2 m/s, and are age dependent.

E´ med cm/s

Measures the early mitral valve annulus velocity at the medial aspect of the annulus and represents the amount of blood that enters the LV during early filling. Normal values are 8-10 cm/s.

E/A

Parameter evaluating the diastolic dysfunction of the left ventricle. It is decreased if ventricular relaxation is impaired. Normal values 1-1.5.

E/E´ med

Is an important parameter estimating LV filling pressures, being comparable to invasive measurements of diastolic function. E´ represents the amount of blood that enters the LV during early filling and E represents the gradient necessary for the blood to enter. A high E/E´ means there is a high gradient for a low shift in volume. E/E´ >13 is diagnostic for diastolic dysfunction and E/E´ <8 is diagnostic for the absence of HFpEF.

ECG – Electrocardiogram

Enddiastolic diameter cm

Diameter of the left ventricle at the end of diastole. A measurement of heart size

ED ms – Ejection duration

Ejection duration, which is the mechanical duration of left ventricuar systole. Depends on heart rate and on systolic and diastolic function.

EDV mL - End diastolic volume

This is the volume in the left ventricle after the completion of diastole before contraction begins. 142 mL (± 21 mL) in healthy 70kg men. (3)

EDV Teich mL

End diastolic volume measured with M mode (Teichholz method).

EF - Ejection fraction%

Ejection fraction is the amount, or percentage, of blood that is being ejected out of the left ventricle with each contraction in relation to the total amount in the left ventricle. 67% (± 4.6%) in 70kg men. (3)

ESC – Europian Society of Cardiology

ESH – Europian Society of Hypertension

ESV mL - End systolic volume

This is the volume remaining in the left ventricle after completion of systole. 47 mL (± 10 mL) in healthy 70kg men. (3)

ESV Teich mL

End systolic volume measured with m- mode (Teichholtz method).

FEV_1 - Forced expiratory volume in 1 second

GMP - Guanosinmonophosphat

GTP - Guanosintriphosphat

Hb mg/dL – Hemoglobin

HbA1c - Hemoglobin A1c

HDL - High density lipoprotein

HF – Heart failure

HFmrEF – Heart failure with middle range ejection fraction

HFpEF – Heart failure with preserved ejection fraction

HFrEF – Heart failure with reduced ejection fraction

HF min^{-1} - Heart frequency

Measured in beats per minute.

HF at rest min^{-1}

Heart frequency before the exercise testing.

LA diameter mm – Left atrial diameter

Left atrial diameter. Normal values are 27-38 for women and 30-40 for men. Higher values stand for left atrial enlargement. (4)

LDL – Low density lipoprotein

LVEF – Left ventricular ejection fraction

LVH - Left ventricular hypertrophy

LV mass m mode g – Left ventricular mass

Measurement of left ventricular mass is performed according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography. Briefly, chamber dimensions and wall thicknesses are acquired from the parasternal long-axis view using targeted m-mode echocardiography at the level of the mitral valve leaflet tips at enddiastole, with the m-mode cursor positioned perpendicular to the septum and the left ventricular posterior wall. End diastolic left ventricular septal and posterior wall thicknesses and internal dimensions are used to calculate left ventricular mass by the validated Devereux formula: left ventricular mass = 0.8 x {1.04 [(left ventricular wall thicknesses + internal dimension)3 - (internal dimension) 3]}+ 0.6 g. Values are normalized to body surface area (BSA). According to ESH/ESC Guidelines on hypertension, values > 115 (men) and 95 (women) represent asymptomatic organ damage.

Maximum workload watt

It is the maximum mechanic effort reached.

Maximum workload % expected

The percentage of the maximum normal values reached adjusted for weight, age and sex. (5)

MBP mmHg - Mean blood pressure

A rough estimate of mean arterial pressure (MAP) is ≃ 2/3 × DBP + SBP/3, a more precise measurement can be obtained by integration of the area under the pressure curve.

aoMBP mmHg

Average arterial pressure during a single cardiac cycle.

bMBP mmHg

Mean blood pressure measured at the brachial artery.

NO – Nitric oxyde

NTproBNP - N-Terminal Prohormone of Brain Natriuretic Peptide

NYHA - New York Heart Association

OSA - Obstructive sleep apnea

Pb mmHg

Amplitude of the backward wave (= reflected wave)

Peak VO_2 mL/min/kg

The amount of O_2 that has been extracted at maximum capacity.

Pf mmHg

Amplitude of the forward wave.

PKG - Protein kinase G

RM - Reflection magnitude

=Pb/Pf. The amount of the forward wave which is reflected.

ROS - Reactive oxygen species

PCWP - Pulmonary capillary wedge pressure

Posterior wall thickness cm

It is also a measurement of LV hypertrophy. <1.1 cm is normal, 1.1-1.3 cm is mild left ventricular hypertrophy, 1.4-1.6 cm is moderate hypertrophy and >1.7 cm is severe hypertrophy. There is some variation by age and gender.

PP mmHg - Pulse pressure

= SBP-DBP.

bPP mmHg

It increases with increasing stiffness and decreases if left ventricular function is severely impaired. A brachial PP >60 mmHg is according to the ESC guidelines a hallmark of asymptomatic organ damage regarding the large arteries in the elderly.

cPP mmHg

The pulse pressure at the aorta derived non invasively

PVW m/s - Pulse wave velocity

Pulse wave velocity. Every contraction of the heart does not only transport the blood column, but also generates a pressure wave called pulse wave. This pulse wave travels along the arterial tree with a certain velocity depending on stiffness of the artery (determinants are among others wall material properties and actual blood pressure). Normal values are age dependent, a cutoff value of 10 m/s has been proposed to represent asymptomatic organ damage

Estimated aoPWV m/s

Aortic pulse wave velocity, estimated with the ARCSolver algorithm from single site pressure waveforms, age and systolic blood pressure.

IVST cm - Interventricular septal thickness

LV septum thickness can be used as a simplified estimate for LV hypertrophy. LV <1.1 cm is normal, 1.1-1.3 cm is mild left ventricular hypertrophy, 1.4-1.6 cm is moderate hypertrophy and >1.7 cm is severe hypertrophy. There is some variation by age and gender.

PVWT - Posterior left ventricular wall thickness

PWA - Pulse waveform analysis

RAAS - Renin angiotensin aldosteron system

RER – Respiratory exchange ratio

SBP mmHg - Systolic blood pressure

aoSBP mmHg - Aortic systolic blood pressure

Systolic blood pressure measured at the ascending aorta.

bSBP mmHg – Brachial systolic bood pressure

Systolic blood pressure measured at the brachial artery.

cSBP mmHG – Central systolic blood pressure

The systolic blood pressure at the aorta derived non invasively.

SBP at rest mmHg

Systolic blood pressure before the exercise testing.

SBP max mmHg

Highest systolic blood pressure reached during exercise.

sGC - Soluble guanyl cyclase

SV mL - Stroke volume

Stroke volume is the volume of blood pumped from the left ventricle in every contraction. EDV-ESV. Normal values 95 mL (± 14 mL) in 70 kg healthy men.(3)

SV Teich mL

Stroke volume measured with M mode (Teichholtz method).

Tr ms – Transit time

Measured as the time difference between the beginning of the pressure wave and the inflection point of the pressure curve, which is characterized by the arrival of the reflected waves. It depends among other parameters on the speed of wave travel and, thus, is a surrogate measure of arterial stiffness.

TGFb - Transforming growth factor beta

VCAM 1 - Vascular cell adhesion molecule 1

VE – Minute ventilation

VSMC - Vascular smooth muscle cell

WHO - World Health Organization

WSA - Wave separation analysis

ABSTRACT IN GERMAN

HINTERGRUND: Die Parameter der pulsatilen Hämodynamik sind mit den linksventrikulären Füllungsdrücken und der diastolischen Dysfunktion assoziiert. Erhöhte Werte können bei vielen Patienten mit Herzinsuffizienz mit erhaltener Ejektionsfraktion (EF) nachgewiesen werden. Der Zusammenhang mit objektiven Parametern der Leistungsfähigkeit ist weitgehend unbekannt. Wir untersuchten ihre Beziehung mit Parametern der maximalen Leistungsfähigkeit (maximum workload) und maximaler Sauerstoffaufnahme (peak VO_2) bei Patienten mit Belastungsdyspnoe, normaler Lungenfunktion und erhaltener EF.

METHODEN: Mittels Tonometrie wurden die Pulswellen an der Radialis gemessen und mittels Fourier Analyse verarbeitet, um zentrale Aortendrücke abzuleiten. Pulswellenanalyse und Pulswellenseparation ergaben Abschätzungen von Vorwärtswellen (Pf) und Wellenreflexion (Augmentationsindex - AIx, Augmentationsdruck - AP, Rückwärtswellenamplitude - Pb). Die aortale Pulswellengeschwindigkeit (aoPWV) wurde mit einer validierten Formel aus Einzelpunktwellenformen geschätzt. Ein Fahrradergometer mit einem Rampenprotokoll wurde für die Ergospirometrie gewählt.

ERGEBNISSE: 66 Patienten wurden eingeschlossen (43 Frauen; mittleres Alter 66 Jahre; 83 % Hypertoniker; mittlerer Body-Mass-Index-BMI 28.3 kg/m^2). Peak VO_2 betrug 17.0 mL/min/kg, die durchschnittlich erreichte maximale Arbeitsbelastung 110 Watt (89 % einer Referenzpopulation). Maximum workload und peak VO_2 zeigten signifikante inverse Beziehungen mit AIx, AP, Pb und aoPWV (r = -0.26 - -0.53). In mehreren adjustierten Regressionsmodellen waren AP, Pf, Pb, brachialer und aortaler Pulsdruck (PP) und aoPWV signifikante unabhängige Prädiktoren für die maximale Leistungsfähigkeit.

DISKUSSION: Die Parameter der pulsatilen Hämodynamik stehen in unabhängiger inverser Beziehung zu objektiven Parametern der Leistungsfähigkeit bei Patienten mit normaler EF.

ABSTRACT IN ENGLISH (1)

BACKGROUND: Pulsatile hemodynamics are associated with left ventricular filling pressures and diastolic dysfunction. Increased values can be detected in many patients with heart failure with preserved ejection fraction (EF). The relationship with objective measurements of exercise capacity remains largely unknown. We investigated their relationship with maximum workload and peak oxygen uptake (peak VO_2) in patients with exertional dyspnea, normal pulmonary function and preserved ejection fraction (EF).

METHODS: Radial waveforms were acquired with tonometry and processed with a transfer function to derive central aortic pressures. Pulse wave analysis and wave separation analysis yielded estimates of forward waves (Pf) and wave reflection (Augmentation Index-AIx, Augmentation Pressure-AP, backward wave amplitude-Pb). Aortic pulse wave velocity (aoPWV) was estimated with a validated formula from single-point waveforms. A bicycle ergometer using a ramp protocol was chosen for ergospirometry.

RESULTS: 66 patients were included (43 females; mean age 66 years; 83 % hypertensives; mean body mass index-BMI 28.3 kg/m^2). Peak VO_2 was 17.0 mL/min/kg, mean achieved maximum workload 110 watts (89 % of a reference population). Maximum workload and peak VO_2 showed significant inverse relationships with AIx, AP, Pb, and aoPWV (r=-0.26 - -0.53). In multiple adjusted regression models, AP, Pf, Pb, brachial and aortic pulse pressure (PP), and aoPWV were significant independent predictors of maximum workload.

CONCLUSIONS: Pulsatile hemodynamics are independently associated with objective measures of exercise capacity in patients with normal EF.

I. INTRODUCTION

Heart failure (HF) becomes an increasing problem in western civilisation. (6) Accordingly so does the entity described as heart failure with preserved ejection fraction - (HFpEF). (7) In heart failure with reduced ejection fraction - (HFrEF) evidence based therapies have improved prognosis. This however is not the case in HFpEF with recent guidelines failing to give Class A recommendations for treatment of that entity. (8) Further research for the deeper understanding of this condition needs to be done as well as methods of identification and management of individuals belonging to this group need to be established.

It is known that pulsatile hemodynamics are related to diastolic dysfunction (9) and may be useful in the diagnostic workup of suspected HFpEF. (10) Our aim was to find the relationship between pulsatile hemodynamics (pulse pressure (PP), wave reflections, aortic stiffness) and exercise capacity using standardized stress test (ergospirometry). The hypothesis was, that there is an inverse relationship between exercise capacity, aortic stiffness and wave reflections. We aimed to investigate the determinants of maximum exercise capacity, among variables derived from echocardiography, or pulsatile hemodynamics, or both in combination, in addition to known determinants as age, gender etc.

1. Heart failure

1.1 Definition

HF is a complex clinical syndrome. It is defined as the condition of the heart failing to deliver oxygen to the body at a rate compatible with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures). (8) Diagnosing HF is difficult, as this depends mostly on the clinical and physical examination. (8) In the recent ESC Guidelines, HF is defined, clinically, as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles and displaced apex beat). (8) They appear as a result of circulatory insufficiency during normal exertion and pulmonary or systemic venous congestion. (8) It is a complex syndrome

resulting from any structural or functional impairment of ventricular filling or ejection of blood. (11) Dysfunction of the myocardium, pericardium, endocardium, valvular disease, arrhythmias, great vessel and metabolic abnormalities can lead to symptoms of HF. (11) The underlying cause is crucial for diagnosis as well as for treatment.

1.2 Signs and symptoms of heart failure

In the following table (Table1.) signs and symptoms of HF are summarized.

Table 1. Symptoms and signs of heart failure (8)

Symptoms	**More typical**	**Less typical**
	Breathlessness Orthopnea Paroxysmal nocturnal dyspnea Reduced exercise tolerance Fatigue, tiredness, increased time to recover after exercise Ankle swelling	Nocturnal cough Wheezing Bloated feeling Loss of appetite Confusion (especially in the elderly) Depression Palpitations Dizziness Syncope
Signs	**More specific**	**Less specific**
	Elevated jugular venous pressure Third heart sound (gallop rhythm) Laterally displaced apical impulse	Weight gain (>2 kg/week) Weight loss (in advanced HF) Tissue wasting (cachexia) Cardiac murmur Peripheral edema (ankle, sacral, scrotal) Pulmonary crepitations Reduced air entry and dullness to percussion at lung bases (pleural effusion) Tachycardia Irregular pulse

		Tachypnoea Cheyne Stokes respiration Hepatomegaly Ascites Cold extremities Oliguria Narrow PP

In addition, other conditions that could explain these findings as a primary volume overload or chronic pulmonary disease should be excluded. (8)

1.3 Heart failure severity classification

The most common classification used for describing the symptomatic status of HF is the NYHA classification from the New York Heart Association. (11) Classes focus on exercise capacity as seen in the Table below. (Table 2.)

Table 2. NYHA Classification of heart failure (11)

Class	**Patient Symptoms**
I Mild	No limitation of physical activity. Ordinary physical activity does not cause fatigue, rapid / irregular heartbeat (palpitation) or shortness of breath.
II Mild	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, rapid/irregular heartbeat or shortness of breath.
III Moderate	Marked limitation of physical activity. Comfortable at rest but less than ordinary activity causes fatigue, rapid/irregular heartbeat or shortness of breath.
IV Severe	Unable to carry out any physical activity without discomfort. Symptoms of fatigue, rapid/irregular heartbeat or shortness of breath are present at rest.

There is poor correlation between symptom severity and ventricular function. Even though there is a clear relationship between the stage and survival, patients with mild symptoms can also have a high risk of hospitalization and death. (12)(13)

Another classification focusing more on the development and progression of HF is by the American College of Cardiology Foundation/American Heart .Association (ACCF/AHA). (11) The stages are progressive. Once you move to a higher stage, regression to an earlier one is not observed. (11) (Table 3.)

Table 3. ACCF/AHA Stages of HF (11)

HF Stage	
A	At high risk for HF but without structural heart disease or symptoms of HF
B	Structural heart disease but without signs or symptoms of HF
C	Structural heart disease with prior or current symptoms of HF
D	Refractory HF requiring specialized interventions

A comparison of both classifications can be seen in the following table. (11) (Table 4.)

Table 4. Comparison of ACCF/AHA Stages of HF and NYHA Functional Classifications (11)

ACCF/AHA Stages of HF		**NYHA Functional Classificaton**	
A	At high risk for HF but without structural disease or symptoms of HF	**None**	
B	Structural heart disease but without signs or symptoms of HF	**I**	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF	**I**	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity does not cause symptoms of HF. Slight limitation of physical activity.

			Comfortable at rest, but ordinary physical activity results in symptoms of HF
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF
D	Refractory HF requiring specialized interventions	**IV**	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

1.4 Types of Heart Failure

Depending on left ventricular function, HF has been devided until recently into two categories: HFpEF and HFrEF. In the newest edition of the European Society of Cardiology (ESC) guidelines (8) an intermediate category has been introduced called heart failure with mid-range ejection fraction (HFmrEF), which is defined by EF values from 40 to 50 %. (8)

EF measured in % is used for assessing the systolic function of the left ventricle. (14) It is the ratio of stroke volume (SV)(End diastolic volume (EDV) – End systolic volume (ESV)) to EDV multiplied by 100 %. (14)

$$EF = \frac{(EDV - ESV) \times 100\ \%}{EDV}$$

If left ventricular function is reduced the ESV increases. In order to maintain SV also the EDV increases through dilation. This results in the reduction of EF. The greater the systolic dysfunction, the lower the EF.

1.4.1 Heart failure with reduced ejection fraction - HFrEF

There are discrepancies as where to set the limit for EF as being reduced. In randomized controlled trials for HFrEF the cut off was set at an EF ≤35 % or ≤40 %. (15) In the recent

ESC guidelines, a cutoff of <40 % has been defined. (8) Beneficial therapeutic effects in terms of improvement in symptoms as well as prognosis of therapy have been shown for this entity. (11)

1.4.2 Heart failure with preserved ejection fraction - HFpEF

In the past HFpEF has been called diastolic HF (DHF), as it was considered to be a disorder of the diastolic function. (16) Nowadays it is believed, that it is a combination of diastolic dysfuction with mild disturbances of systolic function that do not reduce left ventricular ejection fraction (LVEF) (17)(18). Tissue Doppler Imaging studies have demonstrated diastolic and systolic dyssynchrony in HFpEF patients confirming the above theory. (19)

HFpEF is a clinical syndrome resulting from increased resistance in the filling of the left ventricle (LV) leading to symptoms of congestion (11). LVEF is normal or near normal >50 %. (8)

Causes of HF in patients with EF >50% other than HFpEF are cardiomyopathies (e.g. hypertrophic infiltrative), severe valve disease, pericardial disease, right HF caused by right ventricular infarction/arrhythmogenic right ventricular cardiomyopathy and pulmonary arterial hypertension not due to left heart disease or by an obstructive lesion in a big vessel e.g. intracardiac mass or pulmonary vein stenosis. (20) Those have a specific pathophysiology and should not be regarded as HFpEF.

The prevalence of HFpEF is increasing due to demographic changes (aging of the population), increase of lifestyle related risk factors (obesity, diabetes) but also due to a greater awareness of the existence of this condition as well as due to refined echocardiographic techniques. (21)(22) Diagnosing HFpEF is more difficult than diagnosing HFrEF because one basically has to rule out other potential noncardiac causes. (23) In the general population, patients with HFpEF are usually older women with a history of hypertension, obesity and coronary artery disease (CAD). (20) Diabetes mellitus, atrial fibrillation (AF) and hyperlipidemia are also highly prevalent in HFpEF in population based studies and registries. (20)(24) The most important cause of HFpEF is hypertension, with a prevalence of 60 % to 89 %. (25)

About 50 % (range 40-71 %) of patients with HF are considered to belong to this group according to community based studies. (7)(11)(26)(27) This variance is due to different cut

off levels of EF and problems in diagnostic criteria for HFpEF. For our study, we have considered EF as being normal for >50 % in accordance to other studies. (24)(28)(29)(30) and recent ESC and AHA recommendations. (11)(31)

It is uncommon that HFpEF is converted into HFrEF. This might happen due to an incident occurence as myocardial infarction. (32)(33)

According to the recent ESC guidelines the following conditions are required (8):

- The presence of symptoms and/or signs of HF (Table 1.)
- A 'preserved' EF (defined as LVEF ≥50 %)
- Elevated levels of NPs (BNP >35 pg/mL and/or NT-proBNP >125 pg/mL)
- Objective evidence of cardiac structural alterations underlying HF as left atrial volume index (LAVI) >34 mL/m^2 or a left ventricular mass index (LVMI) ≥115 g/m^2 for males and ≥95 g/m^2 for females, or functional alterations as E/E′ ≥13 and a mean E′ (septal and lateral wall) <9 cm/s. Longitudinal strain or tricuspid regurgitation velocity (TRV) are suggested as indirect echocardiographically derived measurements.

1.5 Epidemiological differences between HFpEF and HFrEF

HF is a leading cause of morbidity and mortality in developed countries. (34) Approximately 1–2 % of the adult population in developed countries has HF, with the prevalence rising to ≥10 % among those of 70 years of age and older. (35) The 5 year mortality is similar to the one of many cancers, 50 %. (36)(37)(38) About 23 million people suffer from HF worldwide. (39) 50 % of HF patients have a preserved EF. (7) The prevalence of HFpEF in relation to HFrEF is shown to be increasing. (7) Factors including increased life expectancy as well as improved treatment of hypertension, coronary and valvular disease are allowing patients to survive longer and develop HF. (7) As with advanced age the prevalence of HFpEF risk factors increases, this will be soon the most prevalent HF phenotype. (7) Increased awareness of the existence of HFpEF also contributes to the rise in prevalence. (7) Hospitalizations due to HFpEF have been rising relatively to HFrEF. (40)(39) The pathophysiology of HFrEF is best understood, resulting

in Class AI recommendations regarding treatment. 2/3 of the cases with HFrEF are due to CAD. (41) Probably hypertension and diabetes are contributing factors in many cases. (42) Many other causes including previous viral infection, alcohol abuse, chemotherapy**,** and 'idiopathic' dilated cardiomyopathy are also present. HFpEF seems to have a different epidemiological and etiological profile from HFrEF. (22) Patients with HFpEF are older, more often female and obese. (22) Hypertension is the strongest and most modifiable risk factor to prevent HFpEF. (25) CAD and diabetes on the other hand are leading causes of HFrEF. (42) Diabetes mellitus and insulin resistance may contribute to HFpEF via adverse cell signalling, myocardial apoptosis and fibrosis. (43) Worse outcomes are found with coexistance of chronic obstructive lung disease (31 %) and renal insufficiency (26 %). (44) Female sex as shown by the Framingham study is independently associated with a 2fold increased risk for HFpEF. (45) A reason for the sex differences in HF phenotype could be due to the fact that men more often have HFrEF due to previous myocardial infarction. (46) Another explanation is the difference in response to hypertension in women versus men. (47) In response to hypertension men tend to develop eccentric left ventricular hypertrophy (LVH). (47) Women on the other hand tend to develop concentric LVH. (47) The prevalence of cardiovascular comorbidities in HFpEF is varying among studies, estimating the prevalence of CAD about 20–76 %, diabetes mellitus about 13–70 %, AF about 15–41 % and hypertension about 25–88 %. (22) CAD is less present in HFpEF than in HFrEF but hypertension (associated with arterial stiffness) and AF coexist more often. Chronotropic incompetence might cause symptoms like exercise intolerance and dyspnea. (48) Non cardiovascular comorbidities, as renal impairment, liver disease, peptic ulcers and hypothyroidism are more common in patients with HFpEF. (49) Patients with HFpEF have a better prognosis than those with HFrEF. (50) A metaanalysis showed that risk of death was higher in HFrEF compared to HFpEF but the overall mortality was high in HF regardless of the underlying EF. (50) One reason for the high morbidity and mortality of HFpEF is the lack of evidence based treatments. (49) Two large population based studies following HF patients after discharge from hospital suggested, that there is just a slight difference in the mortality rates of HFrEF and HFpEF patients. (7)(26) In summary, in the community the mortality and hospitalization rates seem to be similar in both types of HF but in clinical trials HFpEF seems to have lower event rates. Selection bias in trials might be the reason for this differences and reevaluation by population or patient based registries needs to be done.

Causes of death in HF patients can be classified into cardiovascular and non cardiovascular. (51) Cardiovascular causes include pump failure, myocardial infarction, sudden cardiac death and cerebrovascular incidents. (51) Non cardiovascular causes are due to renal failure, chronic obstructive pulmonary disease (COPD), respiratory failure, cancer and infections. (52) Cardiovascular death is the reason of mortality for 70-72 % in HFpEF vs 78-94 % in HFrEF. (53)(54) The I–Preserve trial also suggests that the main cause of death in HFpEF is cardivascular with HF and sudden death being the most common. (55)(54) Factors that could predict mortality in HF patients have been analysed in different studies. Most important predictors of mortality in all HF patients have been shown to be low systolic blood pressure (SBP) and elevated renal function tests (serum creatinine and blood urea nitrogen) at the time of presentation. (52) Older age and lower hemoglobin (Hb) levels increase cardiovascular related death risk in patients with HFpEF. (52) Tachycardia was shown to increase hazards of mortality in patients with HFpEF but not in HFrEF. (44) N terminal pro B type natriuretic peptide (NT-proBNP) (56) (even if lower levels in HFpEF) and diabetes mellitus (57) are important factors predicting mortality in HFpEF.

1.6 Hypertension as a cause of heart failure

The most common comorbidity associated with HFpEF is hypertension. (25) Data from the National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of hypertension (diagnosed and undiagnosed) is 75 % for women and 65 % for men ≥65 years of age. (58) No significant change in prevalence of hypertension has been seen in the past decade. The absolute number of hypertensive elderly patients on the other hand has increased due to increased aging of the population (59), accordingly increasing the risk for the development of HFpEF. The frequency of hypertension in patients with HFpEF ranges between 55 and 86 % in population based studies and clinical trials. (27)(45)(60) After the age of 40 the risk of developing HF is twice as high in subjects with BP >160/100 than with <140/90 mmHg (61) according to data from the Framingham study. Hypertension together with aging play a significant role in the development of LVH and diastolic dysfunction (DD). (62) The changes in intrinsic myocardial mechanisms and not LVH or DD alone predispose hypertensive patients to HFpEF. (63) Changes by increased afterload in the microarchitecture and function of cytoskeletal proteins leading to changes in systolic

and diastolic function were shown in animal model studies with LVH (64). In hypertensive patients with normal EF, arterial stiffening was shown to contribute to impaired diastolic function of the regional myocardium. (65)(66) Augmentation index (AIx) was associated with left ventricular diastolic dysfunction as it was correlated with a reduced E/A. (66) Another analysis takes into account the PP, suggesting that it has a greater impact on HF than diastolic pressure, hypothesizing that increased arterial stiffness, which is the underlying pathology in most hypertensive elderly cases may be important in the development of HF. (67) A mechanistic study has shown that arterial stiffness is associated with myocardial wall stress after myocardial infarction. (68) As a consequence, hypertension after myocardial infarction increases the risk of HF through left ventricular remodelling. (68) Arterial remodelling due to elastin degradation, collagen cross linking, geometric changes, changes in endothelial function and neurohumoral signaling are believed to lead to arterial stiffness. (63) The stiffening of central arteries leads to the generation of a wide PP resulting in further elevation of SBP due to the earlier arriving (during systole) reflected wave at the aorta, and accordingly increases SBP. Arterial stiffness is an independent predictor of all cause and cardiovascular mortality in hypertensive patients. (69) Controlling blood pressure improves measures of arterial stiffness and arterial ventricular coupling and helps to prevent HFpEF; however, once HFpEF occurs, antihypertensive medications have not significantly altered HFpEF death outcomes. (70)

1.7 Pathophysiology of HFpEF

1.7.1 General mechanisms

The pathophysiologic understanding of HF has changed over the last 25 years. As mentioned above HF has been divided into two subgroups HFpEF and HFrEF with differences in pathophysiology. (71) Conversion from HFpEF to HFrEF is uncommon and is generally associated with incident myocardial infarction. (32)(33)

Even though the pathophysiologic mechanisms of HFpEF have been approached, definite understanding has not been reached. A better understanding of the pathophysiological processes is needed, as there is no proven treatment found yet. (70) In contrast to HFrEF, the neurohumoral and sympathetic nervous systems do not seem to play a crucial role in

HFpEF as drugs focusing on these mechanisms (β-blockers, ACE inhibitors and mineralocorticoid antagonists) failed to improve the outcome in HFpEF. (8)

Studies based on myocardial specimens from HFpEF patients gave us an insight into the structural and functional abnormalities in HFpEF patients. (72)(73)(74) Remodelling both in the myocardium and the extracellular matrix were found with significant hypertrophy of the cardiomyocytes and interstitial fibrosis (72)(73)(74), translating into increased myocardial stiffness (75) and incomplete relaxation. (76) While HFrEF is characterized by ventricular dilation, sarcomere addition in series and eccentric hypertrophy, HFpEF is characterized by sarcomere addition in parallel and concentric hypertrophy. (77)(78)(79) This leads to a high LV wall mass volume ratio in HFpEF and a low LV wall mass volume ratio in HFrEF. (37)(72)(80) There are also differences at the ultrastructural level: patients with HFpEF have a 50 % larger cardiomyocyte diameter and myofilamentary density than patients with HFrEF. (72) Functional differences are also seen on the cardiomyocytes between the two groups. In vitro cardiomyocyte resting tension is higher in HFpEF leading in combination with the collagen volume fraction to higher in vivo myocardial stiffness. (75) The cytoskeletal protein titin seems to be responsible for this higher resting tension. Increased inflammation and oxidative stress as shown by Westermann and colleagues (74) seem to correlate with diastolic dysfunction. Accordingly, the pathophysiology of HFpEF is a complex entity. The hemodynamic consequences consist of abnormal ventricular arterial coupling, systolic dysfunction despite normal LVEF, pulmonary hypertension, increased LV and arterial stiffness, ventricular diastolic abnormalities resulting in abnormal LV relaxation and raised LV end diastolic pressures. (81) The hemodynamic disturbances often become worse during exercise. Impaired chronotropic response, and impaired atrial functional reserve to exercise might also contribute to this state. (82) (83) LVH and increased LV stiffness due to enhanced fibrosis and shifts in cytoskeletal protein expression and hypophosphorylation as well as disturbances in the ratio of collagen I to III further exacerbate impairment in systolic and diastolic function in HFpEF. (84) Recently growing attention is given to the role of inflammation in HFpEF. (85)

A new paradigm (85) was proposed based on the above data of myocardial remodelling and the role of comorbidities in the pathophysiology of HFpEF. (86)(87) Comorbidities increase oxidative stress and lead to systemic inflammation, endothelial dysfunction and induce reactive oxygen species production (ROS). (85) Inflammation in the endothelium of the coronary microvessels, as well as dysregulation of the signaling between cardiac

endothelium and cardiomyocytes lead to structural and functional changes in cardiomyocytes and extracellular matrix. (85) ROS affect the NO/sGC/cGMP signaling by decreasing soluble guanyl cyclase (sGC) expression levels and decreasing its activation through nitric oxyde (NO). (85) sGC is responsible for the conversion of Guanosintriphosphat (GTP) to Guanosinmonophosphat (GMP). (85) Accordingly protein kinase G (PKG) activity is limited leading to loss of its antihypertrophic effects and increase in resting tension because of titin hypophosphorilation. (85) Furthermore endothelial production of vascular cell adhesion molecule 1 (VCAM 1) allows imflammatory cells migration to the myocardium and secretion of Transforming growth factor beta (TGFb) leading to fibrosis. (85) Endothelial inflammation in the coronary microvasculation leads to stiff cardiomyocites and interstitial fibrosis which leads to increased left ventricular stiffness and to the development of HF. (85) This is being supported by observational studies as better outcomes are seen in statin treated HFpEF patients. (88) A small study of the interleukin 1 antagonist anakinra in patients with HFpEF and elevated C reactive protein (CRP) levels showed improvements in CRP and peak exercise capacity. (89) This novel paradigm gives a central role to the endothelium in the pathophysiology of HFpEF and supports the idea of HFpEF being a systemic disorder. (85) Whether these mechanisms are present in all HFpEF patients or just in the younger subjects without CAD that have been included in the myocardial biopsy studies has to be further investigated. (74) The new HFpEF paradigm aims at restoring myocardial PKG activity. (85)

1.7.2 Functional hemodynamics - LV stiffness

Left ventricular diastolic function depends on the elasticity of the LV, on the energy depending active relaxation and on the atrial contribution. (90) The left ventricular diastolic pressure is depending on the volume of blood in the ventricle and the compliance of the ventricle. During diastole the left ventricle, left atrium (LA) and pulmonary veins form a common chamber. (91) This means that an increase in left ventricular diastolic pressure is leading to an increase in pulmonary venous pressure leading to dyspnea, exercise cessation and pulmonary congestion. (91) In young healthy individuals contractility and the rate of LV active relaxation increase during exercise. (92) This is not the case in HFpEF and appears to play a central role in its pathophysiology. It was shown that patients with HFpEF had significant abnormalities in active relaxation and LV stiffness. (93) In an invasive cardiopulmonary exercise testing in HFpEF patients capillary

wedge pressure (PCWP) was measured as a marker of left ventrucular end diastolic pressure (LVEDP). An increase in LV filling pressure during exercise but not in EDV was observed. This leads to LV filling limitations during exercise and failing of the Frank Starling mechanism. (94) In another study it was shown that active relaxation of the left ventricle during isometric (handgrip) exercise was impaired in a group of HFpEF patients. (82) This could be the reason for the lack in increase of the EDV. (82) Westermann et al. (95) showed that increased left ventricular stiffness in relatively young HFpEF patients contributes to increased end diastolic pressure during handgrip exercise and decreased SV during atrial pacing. Increase in LA contribution in the final stages of LV filling can partly compensate the impaired LV diastolic filling during exercise. (96) This happens until atrial dilatation/failure and atrial fibrillation occurs. Another study showed that some HFpEF patients have reduced atrial function on exercise compared to age matched normal subjects. (83) This failing of atrial contribution during exercise might raise LA pressure during exercise and therefore cause breathlessness. (90) Atrial contribution to filling becomes more important as early diastolic filling is reduced due to impaired suction. (90)

There are many pathophysiological links between increased large artery stiffness and exercise induced diastolic dysfunction. Animal studies showed that a large acute increase in afterload results in slowing of active relaxation and impaired LV diastolic filling. (97) The acute increase in afterload able to cause a slowing of active relaxation is considered to be less in a diseased compared to a healthy heart. (97) This is probably due to poor functional reserve especially with exercise. (97) Phan et al. showed that patients with HFpEF have reduced cardiac energetic reserve that may underlie marked dynamic slowing of LV active relaxation and abnormal arterial ventricular coupling during exercise. (98) 37 patients with HFpEF were recruited according to the AHA criteria with absence of objective evidence of lung disease as seen by functional lung testing.(98) Contractile function was impaired during exercise in HFpEF patients. (98) Impairment in both contractile function and diastole result in a lower SV during exercise. (98) Chronotropic incompetence was also observed. (98)

Exercise intolerance is present in many HFpEF patients even without evidence of volume overload. (28) Pulmonary artery pressures have shown to correlate with left heart filling pressures in early stage HFpEF. (83)

Extra cardiac factors contributing to the pathophysiology of HFpEF include volume overload in conditions such as anemia, renal dysfunction, and obesity. (99) Diabetes, obesity and the comorbidities mentioned afterwards appear to have a greater impact on functional capacity in patients with HFpEF than HFrEF. (100)

1.7.3 Comorbidities in heart failure

Mentz et al. (101) summarised the pathways linking several comorbidities to the progression of HF both with preserved and reduced ejection fraction. Mechanisms as inflammation and worsening congestion together with the sympathetic and renin-angiotensin-aldosterone system activation are highlighted. (101) Comorbidities investigated are as follows:

1. COPD

COPD seen as a proinflammatory state causes endothelial and cardiomyocyte dysfunction together with hypoxia leading to fibrosis and abnormal left ventricular diastolic filling and pulmonary congestion. (101) Elevated LVEDP and b blocker use might also comprise the lung function. COPD is, as mentioned above, more prevalent and has a higher mortality risk in HFpEF. (101)

2. Anemia

Anemia is more prevalent in HFpEF. Adverse LV remodelling and cardiorenal effects together with increased neurohumoral and inflammatory cytokines and the association with poor nutritional status are the potential mechanisms. (102)(103)(104)(105)

3. Diabetes

Diabetes is more prevalent in HFpEF. Even without CAD or hypertension diabetes can lead to the development of myocardial dysfunction. (106) Insulin resistance and hyperglycemia through various mechanisms, including increased free fatty acid concentration, renin angiotensin aldosterone system (RAAS) activation, mitochondrial dysfunction, oxidative stress and abnormal calcium homeostasis lead to myocardial changes. (106)(107) Myocardial fibrosis and collagen changes result in diastolic dysfunction. (108) As HF also increases the risk for diabetes mellitus the relationship between diabetes and HF seems to be bidirectional. (109) The mechanisms explaining the effect of HF on diabetes development or progression of diabetes are not entirely known.

The sympathetic and RAAS activation, with lipolysis and increased cytokine production could be an explanation. (110)(111)

4. Renal dysfunction

The prevalence is similar in HFpEF and HFrEF as is the mortality. (101) Renal dysfunction can lead to worsening of HF through multiple mechanisms, including increased sodium and fluid retention, anemia and inflammation. (101) Uremic toxins, the RAAS and sympathetic activation also play a role. (101) In a recent analysis it was shown that there is an important association between urinary markers of renal dysfunction and the risk for new onset HFpEF but not for HFrEF. (112) On the other side mechanisms related to low cardiac output, inflammation, accelerated atherosclerosis and increased venous pressure in HF may lead to renal dysfunction and cardiorenal syndrome. (101) Its similar prevalence in patients with HFpEF and HFrEF can be partly explained by the big amount of different mechanisms that can lead to renal dysfunction. (101) Diabetic nephropathy is leading to renal dysfunction in HFpEF patients, whereas atherosclerosis contributes due to ischemic and nephrosclerotic etiologies leads to changes in renal function in patients with HFrEF. (113)

5. Sleep disordered breathing (SDB)

The prevalence is similar in both groups, whereas the mortality differences remain unknown. (101) There are two types of SDB and both may coexist in HF patients: obstructive sleep apnea (OSA) and central sleep apnea (CSA). (101) HFpEF patients tend to have OSA, whereas HFrEF patients tend to have CSA. (114) Age is an important risk factor. Men with HF are more likely to have SDB compared with women. Severity is also lower in women than in men. (115) Another risk factor for OSA is an elevated body mass index (BMI), whereas severe LV impairment and atrial fibrillation are more likely to appear in CSA. (116)(117) SDB is proinflammatory, with effects on oxidative stress and sympathetic activation. (118) The occurring hypoxia, arrhythmias, systemic and pulmonary hypertension lead to right ventricular dysfunction and worsen congestion symptoms. (101)

6. Obesity

Obesity as mentioned is more prevalent in HFpEF. (101) The linkage between obesity and metabolic syndrome, glucose intolerance and diabetes partly explain the link between

increased body weight and adverse events. (101) Inflammation plays, as in the coexisting conditions, an important role as well as reduced physical activity and hypertension. (101) In a recent study including 4109 HFpEF patients a U shaped relationship was found between BMI and adverse clinical events. BMI <23.5 or >35 kg/m^2 were both associated with a 27% increase in death or cardiovascular hospitalization, compared with the reference group BMI of 26.5 to 30.9 kg/m^2. (119)

Metz et al. (101) also summarized recommendations for treating the above comorbidities, as follows:

1. COPD

Emphasis is being given on prevention by smoking cessation. Inhaled anticholinergics should be preferred over beta agonist. (101) A multidisciplinary management by both cardiologists and pulmonologists should be aimed. (101) Important in these patients is control of volume overload. (101) Cardioselective beta blockers (metoprolol succinate or bisoprolol) should be preferred. (101)

2. Anemia

There should be a thorough evaluation and treatment of underlying causes of anemia done. (101) Contributing factors such as renal insufficiency and diabetes should be managed. (101) There is no support of applying erythropoetin stimulating agents in HFrEF in studies taken place. (101) Iron deficiency if existing represents a relevant treatment target. (101)

3. Diabetes

Antidiabetic therapies that have been associated with increased risk of HF as thiazolidinediones and dipeptidyl peptidase 4 (DPP 4) inhibitors should be avoided. (101) Other diabetic agents as metformin in the setting of decompensated HF and renal dysfunction should be monitored closely. (101)

4. Renal dysfunction

Appropriate initiation of ACE inhibitors/ARBs with careful clinical monitoring is advised. Volume status presents a key target of intervention. (101) Alternative loop diuretic agents as torasemide or thiazide diuretics might be useful in progressive renal dysfunction. (101)

The management should be multidisciplinary by cardiologists together with nephrologists. (101)

5. Sleep-disordered breathing

Usage of continuous positive airway pressure (CPAP) devices during sleep may be beneficial, in particular as symptom improvement is concerned. (101)

Comorbidity burden increases the risk of hospitalization in HFpEF patients. (120)

2. The role of echocardiography in the assessment of HF

For the evaluation of the systolic and diastolic heart function the two dimensional echocardiogram (echo) is the most commonly used imaging technique. Other functional abnormalities of the heart muscle, valves and pericardium can also be assessed. (11) As mentioned above abnormal relaxation and passive stiffness (decreased compliance of the LV) are two main mechanisms contributing to DD. The relaxation process of the heart depends on calcium reuptake and elastic recoil determined by the viscoelastic properties of the myocardium. (70)

The diastole is divided into the isovolumetric relaxation phase (aortic and mitral valves are closed and LV pressure declines), the early left ventricular filling phase after opening of the mitral valve, the mid diastolic phase and the late atrial filling phase with the LA contraction. (121) In normal hearts the left ventricular filling is predominantly taking place during the early diastolic phase, while in impaired left ventricular relaxation the left ventricular filling becomes more dependent on the atrial contribution. (122) Therefore indicators of diastolic function are LV volumes, LV wall thickness, LA volumes and pulmonary artery pressures. (121) In HFpEF patients LVH, LA enlargement, increased filling pressures and increased pulmonary artery pressures are frequently found. (28)

Main echo based measurements for the diastolic function of the heart are the mitral inflow velocity and the E/A ratio derived from pulse wave Doppler at the 4 chamber view. (123) Mitral inflow includes peak early filling/ early diastolic mitral flow velocity (E wave) and late diastolic filling/ late diastolic mitral flow velocity (A wave). (123) Ventricular relaxation is impaired in diastolic dysfunction leading to a decrease in E velocity and an

increase in A as there is a greater atrial contraction. (123) This leads to a decreased E/A ratio, (124) which is an important echocardiographic parameter for the severity of diastolic dysfunction. (125) In order to distinguish normal from pseudo normal diastolic function, tissue doppler echocardiography can be used. (126) In particular, the ratio between early mitral filling (E) and early mitral (and/or lateral) annular velocity (E´) is helpful. (126) (Figure 1.) It is the most important non invasive estimate of LV filling pressures (126) and has been reported to be comparable to invasive measures for assessment of diastolic function. (127) E depends on LA driving pressure, LV relaxation kinetics, and age. E´ depends mostly on LV relaxation kinetics and age. (126) Accordingly in the ratio E/E´, effects of LV relaxation kinetics and age are eliminated and the ratio becomes a measure of LA driving pressure or LV filling pressure. (29) E/E´>15 is diagnostic of LV diastolic dysfunction and E/E´<8 is diagnostic of the absence of HFpEF. (128) E/E´ ranging from 8 to 15 suggests LV diastolic dysfunction but requires further evaluation. (29) E/E´ is a powerful predictor of survival after myocardial infarction and E/E´>15 is a better prognostic predictor than clinical or other echocardiographic variables. (129) LA volume is also associated with the severity and duration of diastolic LV dysfunction.

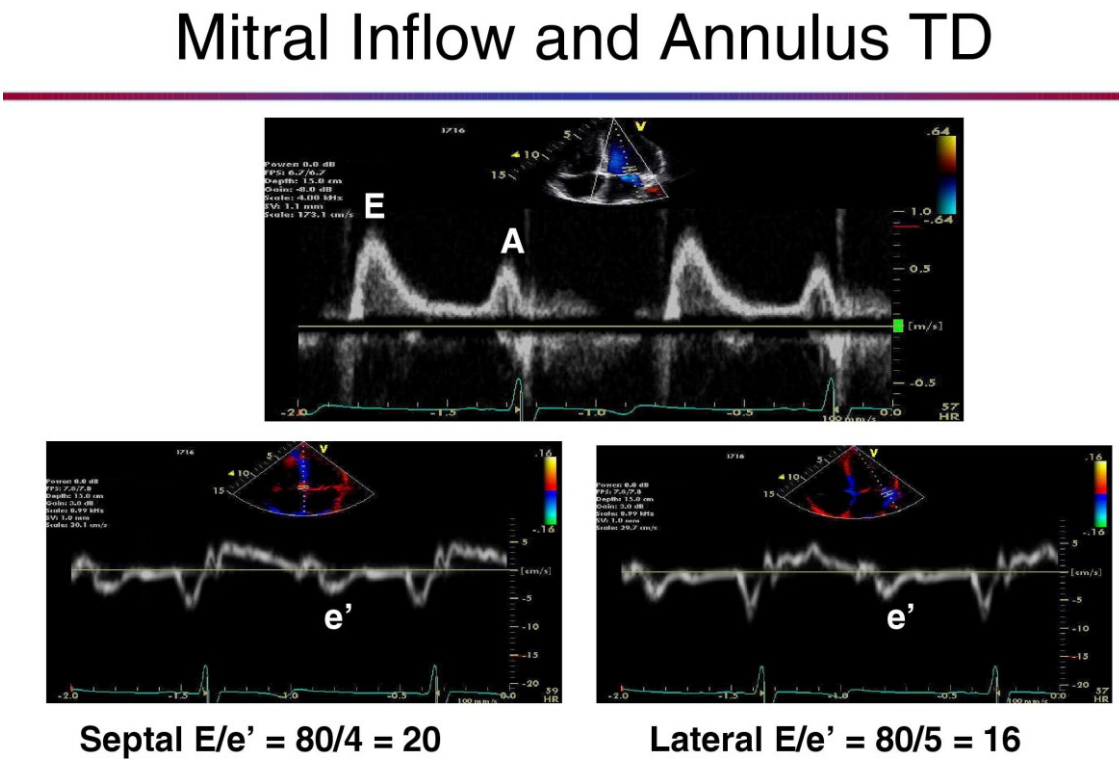

Figure 1. Reproduced from (123) **with permission of Elsevier** Mitral inflow (top), septal (bottom left), and lateral (bottom right) tissue Doppler signals from a 60-year-old patient

with heart failure and normal EF. The E/e′ ratio was markedly increased, using e′ from either side of the annulus.

Systolic function (contractility), is determined by EF, cardiac output (CO) and SV. (130) EF is used for assessing global cardiac function. (130) It is calculated directly from ventricular volumes and is load dependent. (130) Even though EF is not a valid or reliable estimate of true myocardial contractility, it is the most commonly used method for assessing LV function. (130)

In our study, a detailed 2 dimensional and Doppler echocardiography according to the recommendations of the American Society of Echocardiography was obtained in all patients immediately before or after measurement of arterial stiffness/wave reflections, using a Philips iE33 (Philips) machine. (4) For pulsed wave tissue Doppler imaging, the sample volume was located at the medial border of the mitral annulus in the apical 4 chamber view, where we obtained early diastolic mitral annulus velocity (E´). (1)

3. Emphasis on arterial stiffness

3.1 Overview

The arterial wall consists of three layers. The innermost layer called tunica intima or just referred to as intima is made up of endothelial cells. Outside this layer is the tunica media, or media, which is determining the mechanical properties of the wall of elastic arteries. It is made up of smooth muscle cells, elastic fibers and collagen. The outermost layer is known as the tunica externa or adventitia and is composed of connective tissue made up of collagen fibers. The elasticity of the large arteries is dependent on the high proportion of elastin to collagen fibers which is reduced towards the periphery of the arterial tree. (131) The elasticity is not stable, it is changing according to distension pressures on the arterial wall. (131) With higher pressures more inelastic collagen fibres are recruited to bear the load and the elasticity of the arterial wall is reduced. (131)

Arterial stiffness is a term used for structural and functional changes in the arterial system that occur as a consequence of biological aging. A term used synonymously is arteriosclerosis. To describe the functional consequences of arterial mechanics, many researchers nowadays use the term pulsatile hemodynamics. (132) This is related to the

fact that we do not have a laminar or steady circulation (as would occur with a laminar pump), but due to the pulsatile nature of our pump (the heart), blood pressure and blood flow are pulsatile. (132) These pulsatile phenomena are intrinsically related to the mechanical properties of the arteries (and the heart). (132)

In our study, we use parameters as follows:

a) Pulse wave velocity (PWV in m/s) as a direct marker: estimated aortic PWV (aoPWV)
b) Central aortic blood pressure (mmHg): central systolic blood pressure (cSBP), central pulse pressure (cPP), pulse pressure amplification (cPP/peripheral PP)
c) Parameters of the pulse wave analysis: Augmentation pressure (AP mmHg), Augmentation index (AIx %)
d) Parameters of wave separation analysis (WSA): Amplitude of the forward wave (Pf), amplitude of the backward wave (Pb), reflection magnitude = their ratio Pb/Pf (RM)

3.2 Atherosclerosis and Arteriosclerosis

First of all, we have to distinguish the pathology of the arterial wall concerning arteriosclerosis and atherosclerosis. Arteriosclerosis describes the process of thickening and stiffening of the arterial media wall layer which is related primarily to hypertension. Atherosclerosis on the other hand describes a disorder of the intimal layer, endothelial dysfunction and excessive deposition of oxidized lipids. There can be a coexistance of the two processes. Arteriosclerosis can exist without atheromatosis on its own and involves arterial calcification in older individuals with systolic hypertension. (133)

Atherosclerosis It is a pathological condition of the intima, characterized by lipid accumulation, inflammatory cells, vascular smooth muscle cell (VSMC) migration, foam cell development, connective tissue fibres and calcium depositions. (134) Endothelial cell dysfunction and the macrophage and leucocyte infiltration of the arterial wall cause vascular inflammation and atheromatous lesions in the wall of large arteries. (135) This happens due to local oxidation of excessive amounts of low density lipoproteins. (135) Endothelial dysfunction is reversible. It seems that there is an imbalance between vasoconstrictive promoters (e.g. angiotensin II) and vasodilators (NO). (135) If this state becomes chronic the inflammatory vascular changes become irreversible. (135) The

structural changes become more complex and calcification and scarring take over. (135) While repair processes try to stabilize the plaques, the changes stay clinically undetected until the plaques rupture and release calcium, collagen, oxidized lipids and other thrombogenic substances causing embolization, ischemia, organ dysfunction and sudden death. (135) These atherosclerotic changes have complex relationships with arterial stiffness. In a cohort of female twins it was shown that calcified plaques had a correlation to increased stiffness in contrary to non calcified atheromatous plaques. (136) This is consistent with a lack of association between PWV and early stages of atherosclerosis (137)(138) showing that the relation of PWV to vascular calcification might be independent of total plaque burden.

Arteriosclerosis. This term describes a noninflammatory diffuse process that leads to stiffening and dilation of the aorta and its first branches. (139) Pathophysiologically there is a non atheromatous, uniform thickening of the media and adventitia layer with increase in extracellular matrix and vascular smooth muscle cell volume but no significant hyperplasia. (139) There is also loss and fragmentation of elastin fibers which are replaced by collagen and other proteins. The repeated strain on the arterial wall during life by every heart beat seems to be responsible for the breakdown of the elastin, suggesting that some increase in stiffness cannot be completely avoided during ageing. (140) The fact that age related increases in PWV are found in populations with low prevalence of atherosclerosis, suggests that arterial stiffening is caused by the degeneration of the media. (141) There is however variation in the magnitude of age related change between individuals (141) and several indigenous populations do not show an age related increase in PP. (142)

Salt intake affects arterial wall properties. In vitro as well as in animal models, increased sodium concentration leads to vascular smooth muscle cell hypertrophy, increased arterial wall thickness and increased collagen content. (143)(144) It is unclear if these changes are relevant in humans. Cross sectional studies have shown that populations with a high salt intake have greater progression of arterial stiffness. (141) There is a decrease in aoPWV in humans following dietary salt reduction, maybe due to BP reduction.(144)

Widened PP and systolic hypertension are important indicators of morbidity and mortality. It has been shown in the Framingham study that the predominant risk factor for adverse outcomes in older hypertensive patients is SBP. (145) Identification at an earlier age of

those at risk for arterial stiffening could help us to improve our treatment of this high risk group.

3.3 Pulsatile hemodynamics

3.3.1 Pulse wave velocity - PWV

PWV is the speed of travel of waves (pressure, flow) along arteries, and is measured as regional PWV between two defined anatomical points. (146) As the most pronounced effects of aging can be found in the aorta, PWV is commonly measured as carotid femoral PWV (cfPWV), which includes the major portions of the aorta. Other options are direct invasive measurement of aortic PWV (from the ascending aorta to the bifurcation) or non invasive estimation of aortic PWV from single point waveforms (147). PWV relates to the distensibility of the aorta by the Bramwell and Hill equation: $PWV = \sqrt{(V \times \Delta P/\rho \times 1/\Delta V)}$. ρ is the blood density, P is pressure and V volume. PWV is inversely correlated to the elasticity of the aorta, meaning that the stiffer the arteries the higher the PWV. (148) In young healthy individuals the PWV in the ascending aorta is 4-5m/s, in the abdominal aorta it is 5-6 m/s and in the arteria femoralis it is 8-9 m/s. (132) In the elderly it can increase over 12 m/s. (132) As cfPWV measurement is straightforward, PWV by consensus has been called the gold standard measurement of arterial stiffness. (148) PWV is calculated by measuring time taken for a pulse to travel between two points, e.g. the carotid and femoral artery as they are superficial and easily accessible. The aortic PWV is changing with age and other cardiovascular risk factors as hypertension. (132)

PWV is the most widely used technique to estimate the stiffness of the large arteries. It has been used to evaluate the vascular effects of antihypertensive drug therapy. (149)(150)

Arterial stiffness, as measured by cfPWV, is an independent predictor of cardiovascular morbidity and mortality in hypertensive patients, type 2 diabetes, end stage renal disease and in elderly populations. (148) Aortic PWV >13 m/s is a particularly strong predictor of cardiovascular mortality in hypertension. (151) Even after adjustment for classic risk factors, brachial PP and the Framingham risk score, cfPWV keeps its predictive value for cardiovascular events. Data from the Framingham study confirmed this. (152) CfPWV increases at a faster rate in treated hypertensives than in normotensive controls, although it was reduced in those who had good control of their BP. (153)

It was shown to be superior in the diagnosis of diastolic dysfunction to central and brachial blood pressure in older individuals with HFpEF. (154)

In recent guidelines (155) cfPWV has become a vascular biomarker showing manifest end organ damage regarding the large arteries, with a cutoff value of >10 m/s (156).

3.3.2 Pulse pressure - PP

The PP (SBP – DBP) is the most convenient measure of pulsatile hemodynamics. It increases with increasing arterial stiffness and decreases if left ventricular function is severely impaired. It increases with age mostly after the age of 55. In the middle aged and the elderly it is the BP parameter which is closest related to cardiovascular risk. (145)(157)(158) Due to the close relationship between arterial and cardiac function, it could be used to identify patients with HFpEF. (10) A brachial PP >60 mmHg is according to the European Society of Hypertension / European Society of Cardiology (ESC/ESH) guidelines from 2013 a hallmark of asymptomatic organ demage in the elderly. (159) It has been shown in prospective cohort studies in patients without HF that PP is strongly and positively associated with subsequent development of HF. (67)(160) In a recent retrospective cohort study from clinical registry data linked to Medicare claims for 40421 HF patients with 1 year follow up, it was shown that in patients with HF and preserved EF (EF >40 %), there was a significant association between PP and mortality with risk increasing as PP increased, for values PP >50 mmHg. (161) The magnitude of the risk was significantly impacted by SBP. (161) Similar results were observed for setting the EF >50 % to define HFpEF. (161) Benetos and colleagues also came to the result that an increase in PP is an independent parameter for cardiovascular mortality even in normotensive patients aged 40-69 years. (158)

In contrast in HFrEF lower PP independently predicts mortality. (162)

There are however several limitations to brachial PP as a measure of arterial stiffness. It is increasing from the aorta to the periphery due to its dependence on heart rate (HR), arterial geometry and cardiac function (163) which leads to an inverse relationship if the systolic function is impaired. (164) Together with the fact, that it did not show to be superior to other components of blood pressure in some studies (165) concerning risk prediction, more specific methods are needed for the measurement of pulsatile hemodynamics. Those are measurements of PWV and of central BP, as well as measurements of wave reflections.

3.3.3 Pulse waveform analysis - PWA

The pulse wave and its reflections were already used and described in 1905 by the physiologist Otto Frank. He showed that there is a mathematical relationship between pulse wave velocity and arterial stiffness. (166) Already in 1863 as emphasised by Baulmann (167) the physiologist E.J.Marey was able to draw the pulse wave via sphygmography and distinguish between young and older vessels. After the development of the Sphygmomanometer by Riva Rocci, this method was not used for many decades. Nowadays with the new computerized equipment being developed over the last 20 years, we can easily analyze the pulse wave non invasively. (166) PWA gives us important information about functional vessel parameters which could help us in diagnosis, in risk stratification and therapeutic approaches. (166)

When the heart is beating, not only the blood column is propelled, but also a pressure wave is initiated, which travels down the aorta and the arteries at a given speed (PWV), which is much faster than the speed of the blood. (166) At locations with a change of impedance such as bifurcations, the initial pressure wave is reflected. (166)

The extent of the pulse wave reflections depends on the geometry, number and tonus of the arterioles, which are thought to be the major reflection sites. (146) The reflected wave is coming backwards centrally with the same speed (again PWV) and is being added at every point to the initial wave. In young healthy individuals the reflected wave is reaching the aorta in diastole of the same heart cycle in which the antegrade wave was generated. (132)This leads to an increase in the diastolic blood pressure (DBP) and facilitates the perfusion of the coronaries (which occurs during diastole). (132) In older individuals, the reflected wave reaches the ascending aorta in the middle and late systole due to the increased PWV, and, therefore, increases SBP. (132) This leads to the increase in left ventricular afterload and impairs coronary perfusion due to the missing increase in diastolic pressure. These changes in temporal overlap between antegrade and reflected waves explain why an increase in arterial stiffness increases central PP and central BP accordingly. (132)

As mentioned above the pressure wave at every point of the arterial system consists of the sum of the antegrade and retrograde (= reflected) wave. (132) The point on the BP curve where the reflected wave reaches the ascending aorta is called inflection point. (132) The increase in pressure from this point to the maximum SBP is due to the reflected wave and

is called AP. (132) The AP can be expressed as a percentage of the total cPP (AP/cPP × 100) called AIx and resembles the magnitude of the arterial wave reflections. (132) As it derives from a ratio it is dimensionless and expressed as a percentage. It is dependent on arterial stiffness, HR, left ventricular function, gender, height, endothelial dysfunction and peripheral resistance. (168) Due to its dependence on HR AIx is often normalized for a HR of 75/min (AIx75) (169). The AP can be up to 50% of the PP. This strong increase in PP leads to the phenotype of isolated systolic hypertension, which is the predominant form of hypertension in the elderly. (132)

Central BP and AIx/AP can be assessed with the technique of PWA: first, peripheral pulse waves are recorded at the radial or brachial artery. (170) Second, wave forms are calibrated with brachial BP to get absolute pressure values. A so called generalized transfer function, which is based on Fourier analysis of the waves, is then used to generate the central (aortic) pulse waveform. From this, central pressures can be directly derived. For assessment of AIx/AP, derivatives of the waveform are used to identify the inflection point. Then, AIx and AP can be calculated. (171)(172) Pulse wave transit time (time to reflected wave - Tr) is the time from the beginning of the derived aortic systolic pressure waveform to the inflection point.

With increasing age the AIx is increasing as it is reflecting the early incoming wave reflections. This increase is steeper in young years and flattens after the age of 60. (173) This is due to the fact that the reflected wave cannot exceed the primary one. (174)

The invasively measured AP is an independent predictor of cardiovascular events in male patients. (175) Also the non invasively measured AP predicts cardiovascular events in men. (176) A recent meta analysis suggests AIx may be a predictor of cardiovascular disease idependently of peripheral pressures. (177) and that AIx was shown to predict all cause mortality.

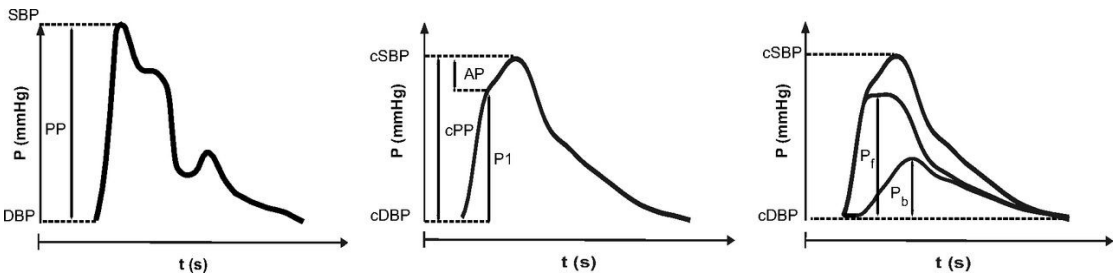

Figure 2. Reproduced from (2) **with permission of Wolters Kluwer Health** Radial (left panel) and aortic (middle and right panels) waveforms and measures of pulsatile arterial function. Left panel, P indicates pressure; SBP, brachial systolic blood pressure; DBP, brachial diastolic blood pressure; PP, brachial pulse pressure. Middle panel, cSBP indicates central systolic blood pressure; cDBP, central diastolic blood pressure; cPP, central pulse pressure; P1, incident pressure wave height; AP, augmented pressure. Right panel, Pf indicates amplitude of forward pressure wave; Pb, amplitude of backward pressure wave.

The AIx has good correlation to cardiovascular risk scores (178) as well as with the plaquescore in under 60 year olds. (179) AIx is also associated with the presence and severity of CAD. (179)

AIx was reported to be an independent predictor of all cause and cardiovascular mortality in end stage renal failure patients. (180)

3.3.4 Wave separation analysis - WSA

There are other options to quantify wave reflections as well. If simultaneously measured pressure and flow waves at the same location are available, a technique called wave separation analysis (WSA) can be utilized, yielding characteristic impedance (Zc), amplitudes of forward (Pf) and backward (Pb) waves and their ratio (Pb/Pf), which is called reflection magnitude (RM). (181) Flow waves can be measured with Doppler echocardiography or magnetic resonance imaging (both are inconvenient and not available during clinical routine) or estimated, using simple triangles or more sophisticated models of the circulation (ARCSolver method). (182) The latter has been validated against the standard Doppler method in different populations. (182)(183) WSA derived measurements of wave reflections are associated with HFpEF and hypertensive organ damage in cross sectional studies. (2) In longitudinal studies, they predict the occurrence of HF and cardiovascular events. (184)(185)

4. Pulsatile hemodynamics and HFpEF

In an ethnically diverse population free of cardiovascular disease at baseline, arterial wave reflections were shown to be an important novel risk factor for CHF. (186) RM was independently associated with incident cardiovascular events (CVE) and strongly

associated with incident CHF, whereas AIx was a predictor for hard CVE. (186) In the general population E/E´ ratio increases significantly with AP, cPP, PWV. (187) AIx as a marker of wave reflections and arterial stiffness was shown to be an independent determinant of LV diastolic dysfunction, as diagnosed by Doppler echocardiography in untreated patients with essential hypertension. (66) In a prospective study with the aim to investigate whether wave reflections are elevated in patients with diastolic dysfunction 235 patients with normal systolic function who underwent coronary angiography were included. (188) Based on natriuretic peptides and invasively measured filling pressures, they were categorized as having normal diastolic function or diastolic dysfunction. It was shown that those categorized as having diastolic dysfunction had higher wave reflections (AP) compared to controls. (188) In a study with 336 middle aged and elderly patients undergoing cardiac catheterization PWV was assessed invasively and wave reflections by radial tonometry. (9) Filling pressures were estimated using the E/E´ ratio and were significantly associated with increased wave reflections and PWV. (9) In multivariable analysis, only AIx and characteristic impedance (Zc) significantly predicted E´, even after adjustment for age. (9) The associations between diastolic dysfunction/HF and increased PWV/increased central pressures have been confirmed in a series of studies. (82) (154)(189)(190) baPWV was shown to be closely associated with early mild DHF in the general middle aged population suggesting that arterial stiffness is associated with mild DHF. (191) This was independent of age, male gender, BMI, posterior left ventricular wall thickness (PVWT) , interventricular septal thickness (IVST), E/E′ ratio, left ventricular mass index (LVMI), and high BP. (191) Older patients with HFpEF have increased arterial stiffness beyond what occurs with normal aging which contributes to their severe exercise intolerance. (192)

5. Exercise testing

5.1 Overview

Exercise testing as performed by ergospirometry is a diagnostic tool used for the assessment of cardiopulmonary and metabolic exercise capacity qualitatively as well as quantitatively. (193) By measuring ventilatory gases during physical exercise we can assess the reaction and function of the cardiopulmonary system and metabolism. (194)

It has become an important tool in predicting outcome in chronic HF patients by objectivally assessing exercise capacity. (193)(195) LV diastolic function is useful for determining exercise capacity, as an excessive rise in pulmonary capillary wedge pressure is the main cardiac cause for exertional dyspnea. (196)

In a recent study it was shown that even among patients with normal clinical examination, echocardiography, and resting haemodynamics, many patients could develop pathologic elevations in filling pressures during exercise characteristic for HFpEF. (197)

Maximum oxygen uptake (VO_2) at maximum exercise is considered the best index of aerobic capacity and cardiorespiratory function. (198) It is resembling the highest rate of transport and use of oxygen. It is being calculated according to the Fick`s principle as the product of cardiac output (CO) and the arteriovenous oxygen difference (a-vDO_2):

$VO_2max=COmax \times a\text{-}vDO_2max$

5.2 Primary ventilatory measurements (194)

There are 4 values directly measured by spirometry: a) respiratory flow, b) frequency of breathing, c) difference of oxygen concentration ΔO_2 and d) difference of carbon dioxid concentration ΔCO_2.

a) Ventilatory (respiratory) flow
   Enables the compilation of the flow/volume graph
b) Frequency of breathing f
   At rest between 12-20 per minute, increases during exertion about 3 times. The maximal reached frequency of breathing shows whether the limit of exertion is reached. It is no indicator of increased or decreased performance but of symptom limited exertion.
c) Difference of oxygen concentration ΔO_2 between exspiratory and inspiratory air. This correlates with the amount of oxygen consumed by the body.
d) Difference of carbon dioxid concentration ΔCO_2 between exspiratory and inspiratory air. Concentration of inspiratory air is 0. The measured CO_2 derives from cell metabolism.

5.3 Derived ventilatory measurements (194)

a) Oxygen uptake (VO_2)

VO_2= VE × ΔO_2. VO_2 whereas VE= Minute ventilation

VO_2 rises linearly with increasing work load and reaches the maximum (VO_2max) at the symptom limiting exertion point. VO_2max as mentioned above represents most reliably the maximum capacity of the cardiorespiratory and metabolic system. It is the amount of O_2 that is being extracted from the inhaling gas per time unit. (199). The higher the capacity the higher the VO_2max. There is, as with VE, no typical value for exertion. It is being influenced by anthropometric parameters as gender, age, height and weight. For a better comparability it is standardised on bodyweight (mL/min/kg).

The original definition of VO_2max includes the levelling off point, meaning that there is a point where there is no further increase in VO_2 with more intense performance. If there is no levelling off it is called peak VO_2. There have been discontinuously treadmill protocols used for the original definition with breaks of different lengths. (194) Nowadays with the usage of continuously protocols and the breath by breath analysis there have been many studies that could not show the levelling off phenomenon and VO_2max is set equal to peak VO_2. (194) This is the oxygen uptake measured at the end of the strain. Normal values during exercise should be for males = -0.42 × age (years) + 58 and females = -0.35 × age (years) + 46 (mL/min/kg) according to an expert consensus paper that analysed several reference values in healthy adults of the age of 40 and above. (200) For a man of 70 years of age this would mean VO_2max around 28 mL/kg/min. Values under 10mL/kg/min are associated with an impaired prognosis, particularly in HF. (201) Its predictive value is valid only if exercise capacity is limited by HF. It must be seen in the setting of the patients age and gender as it is influenced by them.

b) Carbon dioxide output (VCO_2)

VCO_2= VE× ΔCO_2. VCO_2 is the amount of CO_2 that is being exhaled per time interval. There is no typical value for VCO2 at the exertion point, the higher the capacity the higher the VCO2.

c) Respiratory exchange ratio (RER)

RER= VCO_2/VO_2. The RER shows to which part lipids or glucose are used for aerobe metabolism. In the steady state the RER depends on the metabolic substratum. If just lipids are used RER is 0.7 if just glucose is metabolised RER is

1. At rest it is 0.82-0.85. At high intensity strains the lactate production is higher and the CO_2 levels increase due to release of the bicarbonate puffer. CO_2 production is higher than O_2 intake which leads to RER values higher than 1. RER >1 indicates that someone has reached the metabolic exertion. It is independent of the level of fitness, well trained and untrained individuals reach RER >1 just if they reach their individual exertion point.

d) Breathing Reserve (BR)

This parameter helps us estimate if the ventilatory capacity has come to the limit.

BR is normally >20 %. If it is less than 20 %, the ventilatory capacity has come to the limit.

5.4 Primary hemodynamic values (194)

a) HR

The autonomic nervous system is responsible to the adjustance of the cardiovascular system during exercise. The HR is dependent on age, type of activity, medication, cardiac diseases but not on gender and or exercise capacity. The maximal HR is calculated with:

HRmax= 220 - age

b) BP

Is measured to identify hypertension at rest or at exercise. Normal values at rest are <140/90. For the values during exercise the following formula can be used:

SBP = 145 + 1/3×W +1/3 × age

DBP = <100mmHg independently of the working load

If the BP measurements are above the estimated values the subject is considered to have exercise induced hypertension.

If the SBP is decreasing more than 10 mmHg during continuous increase in workload, the protocol should be discontinued. This is a marker of myocardial exercise insufficiency.

5.5 Values at exertion (194)

a) Performance parameters

   Values with no upper limit, getting higher with higher performance. The maximum values resemble the exercise capacity

   a) Maximum workload: maximum mechanic effort
   b) VO_2max: maximum aerobic exercise capacity

b) Values resembling the maximum limited exertion

   They have a fixed upper limit and resemble exertion. They are reached if capacity has come to its limit regardless of the level of fitness and high or low exercise capacity.

   a) For circulation: HR (220-Age)
   b) For ventilation: f >35
   c) For muscle metabolism: RER >1

6. Exercise capacity and HF

Exercise capacity decreases while HF is progressing. (202) The decrease in maximal exercise capacity is associated with decreased survival. Cardiac output can be normal at rest but cannot increase adequately during exertion. (203)

Training in HFpEF patients is shown to increase peak VO_2 but without alterations in arterial stiffness regarding endurance training as shown by a randomised controlled trial. (204) This suggests, that muscle adaptations and improvement of oxygen transport and utilization might lead to the improvement in exercise capacity. (205)(206) Interval training on the other hand showed improvement of diastolic function. (207)

7. Aim of our study: Relationship between pulsatile hemodynamics and exercise capacity/HFpEF

Our aim was to find the relationship between pulsatile hemodynamics at rest and exercise capacity using standardized stress test (ergospirometry). (1) The hypothesis is that there is

an inverse relationship between exercise capacity and aortic stiffness and wave reflections. (1)

II METHODS OF EVALUATION

1. Patients

The data collection took place from 3/2011 to 1/2016.(1) 66 patients with exertional dyspnea and normal ejection fraction were included in our study. (1) Exclusion criteria were impaired systolic function (EF <50 %), valvular heart disease, significant CAD, rhythm other than sinus rhythm at the time of examination, more than mildly impaired pulmonary function, other reasons for exercise impairment (e.g. severe anemia), patients not reaching metabolic exertion (i.e. RER needed to be >1)(208) at maximum workload and patients in whom there was a pulmonary limitation of exertion (i.e. BR <20 % at the end of the exercise test). (1)(208) All patients underwent assessment of pulsatile hemodynamics, cardiac catheterization, echocardiography, and ergospirometry. (1) The study was approved by our regional ethics committee (Ethikkommission für das Land Oberösterreich) - EK number 248. (1)

Hypertension was defined as repeated measurements ≥140 mmHg systolic and/or ≥90 mmHg diastolic BP, or permanent antihypertensive drug treatment. (1) Diabetes mellitus was defined as a fasting blood glucose concentration ≥126 mg/dL and HbA1c ≥6,5 % or antihyperglycemic drug treatment. (1)We defined significant CAD as at least one ≥50% diameter stenosis in at least one major coronary vessel (1)

2. Pulsatile hemodynamics

We used the Sphygmocor device for quantifying pulsatile hemodynamics. (Atcor Medical, Australia). (1) With this device high sequential pressure waveforms are recorded at the radial artery with a high fidelity tonometer (Milar instruments, Houston, Texas) for assessment of central pressures, PWA (yielding AugP and AIx) (170) and WSA (yielding Pf, Pb, RM). (181) PWA was performed with the SphygmoCor software system Version 9 (AtCor Medical, Sydney, Australia), WSA with the ARCSOlver method. (184) Brachial

BP was measured with a validated, automated, oscillometric, sphygmomanometer (Omron M5-I, Omron Healthcare, Kyoto, Japan) (209) and used to calibrate the radial waveforms. Aortic pulse wave velocity was estimated from single point waveforms, using the ARCSolver algorithm as this has been shown to be in good correlation to cPWV. (210) Tr as mentioned above is the time from the beginning of the derived aortic systolic pressure waveform to the inflection point and has been shown to be related to PWV-a shorter Tr will lead to a higher PWV. (1) Pulsatile hemodynamics were assessed by nurses not involved in other aspects of the study. Measurements were taken within 3 days apart from exercise testing. (1) Patients had to be sitting for at least 5 minutes in a quiet, temperature controlled room (22 ± 1 °C) before measurements. (1)

3. Cardiopulmonary exercise testing

We used the Ergostik unit (Geratherm company, Germany) for the ergospirometry. Ventilatory gases are measured by the spirometer. (1) A mask is firmly placed over the mouth and nose of the proband. A volume and gas sensor is connected to the mask allowing measurement of the ventilated volume as well as analysis of the gas mixture during expiration. Minute ventilation, oxygen uptake (VO_2), and carbon dioxide output (VCO_2) were measured with rapidly responding gas analyzers breath by breath during the test, the other cardiopulmonary variables were derived according to standard guidelines. (211) Peak VO_2 and peak RER were assessed as the highest 30 second average during exercise. (1) Maximum exercise capacity was expressed as maximum workload and as peak VO_2. (1) The workload is measured by the ergometer. The bicycle is chosen as the ergometer due to its advantages over the treadmill in aspects of space, artefacts, safety and standardisation. The ramp protocol chosen is individualized in order to reach the maximum exercise capacity within 8-12 minutes. (1) 12 lead electrocardiograms were obtained at rest, and continuously during the study. (1) bBP was measured at rest, each 2 minutes during exercise, and for at least five minutes during the recovery phase. (1)

4. Echocardiography

In our study, a detailed 2 dimensional and Doppler echocardiogram according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography (4) was obtained in all patients immediately before or after measurement of arterial stiffness/wave reflections, using a Philips iE33 (Philips) machine. In the absence of segmental contraction abnormalities, LA diameter and left ventricular dimensions (to calculate SV with the Teichholtz formula (4) and left ventricular mass with the Devereux formula (4)) were assessed with m mode in the parasternal long axis view. For pulsed wave tissue Doppler imaging, the sample volume was located at the medial and/or lateral border of the mitral annulus in the apical 4 chamber view, where we obtained early diastolic mitral annulus velocity (E´). (1)

5. Cardiac catheterization

In all patients, significant CAD was ruled out by invasive coronary angiography on our monoplane or biplane angiography system. (1) (Siemens Artis Zee with AXIOM Sensis hemodynamic recording system, Siemens Healthcare, Erlangen, Germany).

6. Statistics

Continuous variables are expressed as mean values (standard deviation), categorical data as numbers (percentages). Univariate associations between measures of exercise capacity on the one hand and demographic variables, pulsatile hemodynamics and echocardiographic measurements on the other hand were examined using Pearson´s correlation coefficient. (1) Next, stepwise multiple linear regression models for predicting parameters of exercise testing were calculated, including age, gender, BMI and E/E´ in addition to parameters of pulsatile hemodynamics. (1) Statistical analyses were performed using the Statistica 6.0 (StatSoft, Tulsa, OK), and MedCalc 9.2 (MedCalc software, Mariakerke, Belgium). (1) For all tests, a P value of <0.05 was considered significant.

III RESULTS

1. Baseline characteristics

1.1 Anthropometric and laboratory data

Among the 66 individuals included, 23 (35 %) were male and 43 (65 %) were female. (1) Mean age was 66 years (ranging from 36 to 88). (1) Mean BMI was 28.3 kg/m^2 (19 to 41). (1) 83 % had hypertension, 13 % were diabetics, 7.5 % were smokers. 3 % had previous MCI, 1.5 % had previous stroke and 10 % were diagnosed as having CAD (without significant coronary obstruction at the time of the coronary angiogram). (1) At the moment of investigation, all of them were in sinus rhythm, 8 (12 %) had minor mitral regurgitation, 6 (9 %) had mild lung disease and 5 (7.5 %) a mildly abnormal pulmonary function test at rest. (1) Mean plasma level of NT pro BNP was 187 pg/mL (ranging from 11 to 874), mean Hb was 14.1 g/dL (ranging from 11.8 to 17.8). (1) No patient had a pulmonary limitation of exercise capacity. (Table 5., Table 6.) (1)

Table 5. Baseline characteristics/anthropometric data (1)

Categorical parameters	**number**	**Percentage**
Male gender	23	34.85
Hypertension	55	83.33
Diabetes	9	13.63
Smokers	5	7.57
Previous MI	2	3.03
Previous stroke	1	1.52
Sinus rhythm	66	100
CAD	7	10.6
MI I-II	8	12.12
Mild lung disease	6	9.09
Mildly impaired pulmonary function	5	7.57

Table 6. Baseline characteristics/laboratory data (1)

Descriptive statistics baseline characteristics	**Mean**	**SD**	**Min**	**Max**
Age years	66	11	36	88

Height cm	166	10	148	193
Weight kg	78	16.6	51	120
BMI kg/m^2	28.3	5.2	19	41
BSA m^2	1.9	0.2	1.5	2.5
NT pro BNP pg/mL	187	182	11	874
Total cholesterol mg/dL	209	42	116	283
LDL mg/dL	118	34	52	202
HDL mg/dL	62	21	25	125
Triglycerides mg/dL	146	91	43	615
Fasting blood glucose mg/dL	102	16	65	139
HBA1c %	6.1	0.7	5	10.1
Creatinine mg/dL	0.9	0.2	0.5	1.3
Hb g/dL	14.1	1.2	11.8	17.8
Natrium mmol/L	139	3	130	145
Waist circumference cm	99.4	14	71	129

1.2 Pulsatile hemodynamics

At rest, mean brachial BP was mildly elevated (144/82 mmHg). The other variables of pulsatile hemodynamics are given in Table 7. (1)

Table 7. Pulsatile haemodynamics via tonometry (1)

Descriptive statistics sphygmocor	**Mean**	**SD**	**Min**	**Max**
HR min^{-1}	60	8,5	38	83
bSBP mmHg	144	16	119	183
bDBP mmHg	82	9	58	100
bMBP mmHg	104	10	83	127
bPP mmHg	62	15	20	90
cSBP mmHg	135	15	106	179
cDBP mmHg	83	9	60	101
cPP mmHg	52	14	18	85
AP mmHg	19	9	-5	40

AIx %	34	12	-14	63
AIx75 %	27	10	-10	49
Tr ms	132	12	98	163
Pf mmHg	33	8.5	11.5	52
Pb mmHg	22	6.3	7	36.5
RM	0.66	0.09	0.38	0.83
Estimated aoPVW m/s	9.7	2	5	14

The invasively (during cardiac catheterization) measured pressures are shown in Table 8.

Table 8. Pulsatile haemodynamics via cardiac catheterization (1)

Descriptive statistics Angio	**Mean**	**SD**	**Min**	**Max**
aoSBP mmHg	130	22	82	194
aoDBP mmHg	60	13	41	87
aoMBP mmHg	89	16	66	126

1.3 Echocardiographic measurements

Mean EF was 70.4% (SD 9.4). Early diastolic function was impaired in most patients (mean E´medial annulus was 5.3 cm/s), and filling pressures were increased in many patients (mean E/E´was 11.9). The other parameters are shown in Table 9. (1)

Table 9. Echocardiographic measurements (1)

Descriptive statistics Echo	**Mean**	**SD**	**Min**	**Max**
SV Teich mL	78	20.9	38	139
E´ med cm/s	5.3	1.6	3	10.4
E/E´ med	11.9	2.7	5.8	17
E/A	0.82	0.3	0.4	1.6
LV mass mmode g	198	60.3	109	322
IVST cm	1.1	0.2	0.7	1.8
EDV Teich mL	112	30.5	50	194
ESV Teich mL	35	14.8	8.3	92

EF Simpson %	70	9.4	25	85

1.4 Angiographic measurements

Mean EF measured during invasive angiography was 76% (SD 8)(Table10.). (1)

Table 10. Angiographic measurements (1)

Descriptive statistics Angio	Mean	SD	Min	Max
EF %	76	8	48	92
EDV mL	120.9	29.8	49	185
ESV mL	29.1	11.4	7	57
SV mL	91.7	24.4	32	141

1.5 Ergospirometric measurements

Mean peak VO_2 was 17.0 mL/kg/min (SD 6.11), corresponding to a predicted value of 84.8% (SD 33). The mean maximum workload was 104.5 watt (SD 52.3), corresponding to a predicted value of 80.1% (SD 28.8). (Table 11) (1)

Table 11. Ergospirometric parameters (1)

Descriptive statistics ergospirometry	Mean	SD	Min	Max
peak VO_2 mL/min/kg	17	6.11	6.2	41.2
peak VO_2 % predicted	84.8	33.0	18.8	155.0
Maximum workload watt	104.5	52.3	34	273
Maximum workload % predicted	80.9	28.8	28	184
SBP at rest mmHg	120	15	91	162
DBP at rest mmHg	82	13	56	114
SBP max mmHg	185	26	135	279
DBP max mmHg	90	17	51	139
HR at rest min^{-1}	71	12	47	101
HR max min^{-1}	127	22	81	182
RER	1.15	0.09	0.96	1.4

1.6 Gender differences

In the following tables we can see the statistical significant differences between the two sexes. No statistical difference regarding age was found. Differences in height and weight as one could naturally expect were seen with men being taller and heavier. Men had as a natural consequence higher Hb levels and creatinine (Crea) levels (Table 12.)

Table 12. Differences in the baseline characteristics/laboratory data

Descriptive statistics baseline characteristics	Men Mean N = 23	Women Mean N = 43	Men SD	Women SD	p value
Height cm	**175.6**	**160.4**	**7.5**	**6.2**	**0.000000**
Weight kg	**87.7**	**72.9**	**13.8**	**15.8**	**0.000351**
BSA m^2	**2.05**	**1.79**	**0.18**	**0.2**	**0.000002**
log NT pro BNP pg/mL	**1.91**	**2.17**	**0.48**	**0.38**	**0.029**
HDL mg/dL	**54**	**67**	**22**	**20**	**0.0227**
Creatinine mg/dL	**0.99**	**0.8**	**0.14**	**0.19**	**0.003**
Hb g/dL	**15.1**	**13.7**	**1.26**	**0.88**	**0.000003**

Parameters of pulsatile hemodynamics as AP, AIx %, AIx 75, Pb, RM, ED were all higher in women than in men as described in the literature. This is partially related to shorter body height in women, leading to earlier arrival of reflected waves in women. This is also in accordance with the finding that Tr time is shorter in women than in men. In contrast, estimated aortic PWV (aoPVW ARCSolver) did not differ between men and women. (Table 13.)

Table 13. Gender differences in pulsatile haemodynamics via tonometry

Descriptive statistics pulsatile hemodynamics	Men Mean N = 23	Women Mean N = 43	Men SD	Women SD	p value
AP mmHg	**13**	**22**	**7.28**	**8.65**	**0.00016**

AIx %	**25**	**39**	**13**	**9**	**0.000002**
AIx75 %	**19**	**31**	**19**	**7**	**0.000000**
Tr ms	**141**	**128**	**9**	**11**	**0.000016**
Pb mmHg	**19**	**23**	**5**	**7**	**0.044**
RM	**60**	**69**	**9**	**7**	**0.000145**
ED ms	**315.5**	**331.33**	**25.33**	**22.93**	**0.0135**
Estimated aoPWV m/s	**9.5**	**9.8**	**2.3**	**1.8**	**0.47**

As expected oxygen uptake indicated by VO_2 was at rest and at exertion higher in men then in women. The same was shown for the mechanical effort indicated by load. SBP at rest did not differ at rest, but men reached higher SBPs with exertion than women. HR at rest did not differ but tended to be higher in men with maximum exertion (Table. 14)

Table 14. Gender differences in ergospirometric parameters

Descriptive statistics ergospirometry	**Men Mean (N = 23)**	**Women Mean (N = 43)**	**Men SD**	**Women SD**	**p value**
VO_2 at rest mL/min/kg	**3.19**	**2.66**	**0.76**	**0.9**	**0.02**
Peak VO_2 mL/min/kg	**20.8**	**15**	**7.1**	**4.5**	**0.00016**
Peak VO_2 predicted %	**24.5**	**17.9**	**4.5**	**3.7**	**0.00000**
Maximum workload watt	**154**	**79**	**55**	**26**	**0.000000**
Maximum workload predicted%	**99.7**	**70.35**	**32.056**	**20.77**	**0.000179**
SBP at rest mmHg	**122**	**119**	**16**	**14**	**0.41**
SBP max mmHg	**198**	**177**	**27**	**22**	**0.0018**
HR at rest	**70**	**68**	**11**	**12**	**0.64**

Men had larger LA diameter, LV mass, EDV, septal and posterior wall thickness and even after accounting left ventricular mass per BSA they had higher values than women (Table 15.).

Table 15. Gender differences in echochardiographic measurements

Descriptive statistics echocardiography	Men Mean (n=22)	Women Mean (n=43)	Men SD	Women SD	p value
IVST cm	**1.19**	**1.05**	**0.25**	**0.21**	**0.03**
Posterior wall thickness cm	**1.16**	**1.05**	**0.2**	**0.2**	**0.0457**
LA diameter cm	**4.03**	**3.56**	**0.405**	**0.498**	**0.000517**
LV mass M mode g	**240.2**	**178.6**	**64**	**48.2**	**0.000155**
LVM per BSA g/m^2	**118.6**	**99.5**	**33**	**23.3**	**0.014**
EDV Teich mL	**127.2**	**105.1**	**37.9**	**23.8**	**0.007756**
ESV Teich mL	**42.1**	**31.5**	**18.1**	**11.7**	**0.009**
End diastolic diameter cm	**5.1**	**4.7**	**0.7**	**0.6**	**0.0116**

2. Univariate relationships with exercise capacity

2.1. Anthropometric and laboratory measurements

Age was inversely associated with exercise capacity (peak VO_2, maximum workload) as was NT proBNP. In contrast body height was directly associated with exercise capacity (peak VO_2, maximum workload). BMI was inversely associated with peak VO_2 . (Table 16) (1)

Table 16. Univariate associations between measurements of exercise capacity and age, body height, BMI, and NT proBNP (1)

Variable	Age	Height	BMI	NT-proBNP
Peak VO_2 mL/min/kg	-0.37	0.35	-0.4	-0.32
Maximum workload watt	-0.48	0.62	n.s.	-0.50
Values are Pearson´s correlation coefficients. Only values with p <0.05 are shown.				

2.2 Echocardiographic parameters

SV was directly correlated with exercise capacity (peak VO_2 and maximum workload). LV mass was directly associated with maximum workload. E/A was not associated with exercise capacity. E´ was directly associated with exercise capacity (peak VO_2, maximum workload). E/E´ was inversely associated with exercise capacity (peak VO_2, maximum workload). (Table 17.) (1)

Table 17. Univariate associations between measurements of exercise capacity and echocardiographic parameters (1)

Variable	SV (Teich)	LV mass mmode	E/A	E´	E/E´
Peak VO_2 mL/min/kg	0.37	n.s.	n.s.	0.35	-0.5
Maximum workload watt	0.37	0.37	n.s.	0.27	-0.4
Values are Pearson´s correlation coefficients. Only values with p<0.05 are shown.					

2.3 Pulsatile hemodynamics

Brachial BPs (SBP, DBP) at rest were not related to exercise capacity. Brachial and central PP were inversely related to maximum workload. Measures of wave reflections and estimated aoPWV were inversely related to most measures of exercise capacity. (Figure 3.) Tr was directly related to most measures of exercise capacity. (Table 18.) (1)

Table 18. Univariate associations between measurements of exercise capacity and pulsatile hemodynamics (1)

Variable	Peak VO_2 mL/min/kg	Maximum workload watt
bPP mmHg	n.s.	-0.28
cPP mmHg	n.s.	-0.41
AP mmHg	-0.3	-0.54
AIx%	n.s.	-0.5
AIx75 %	-0.31	-0.57
Tr ms	0.41	0.54
bDBP mmHg	n.s.	0.25
Pf mmHg	n.s.	-0.46
Pb mmHg	-0.26	-0.43

RM	n.s.	-0.33
Estimated aoPVW m/s	-0.36	-0.49
Values are Pearson´s correlation coefficients. Only values with p<0.05 are shown.		

When dividing the group into subgroups of men and women there were differences observed in correlation between those groups. Whereas in women, most inverse relationships between pulsatile hemodynamics and exercise capacity could be observed, in men there was only an inverse relationship between the maximum exercise capacity, expressed as maximum workload, and estimated aoPWV. (Table 19., Table 20.)

Table 19. Univariate associations between measurements of exercise capacity and pulsatile hemodynamics in men

Variable	Maximum workload watt
Tr ms	0.48
Estimated aoPVW m/s	-0.6
Values are Pearson´s correlation coefficients. Only values with p<0.05 are shown.	

Table 20. Univariate associations between measurements of exercise capacity and pulsatile hemodynamics in women

Variable	Peak VO_2 mL/min/kg	Maximum workload watt
bPP mmHg	n.s.	-0.49
cPP mmHg	n.s.	-0.47
AP mmHg	n.s.	-0.41
Tr ms	n.s.	0.41
bSBP mmHg	n.s.	-0.41
Pf mmHg	n.s.	-0.46
Estimated aoPVW m/s	-0.39	-0.63
Values are Pearson´s correlation coefficients. Only values with p<0.05 are shown.		

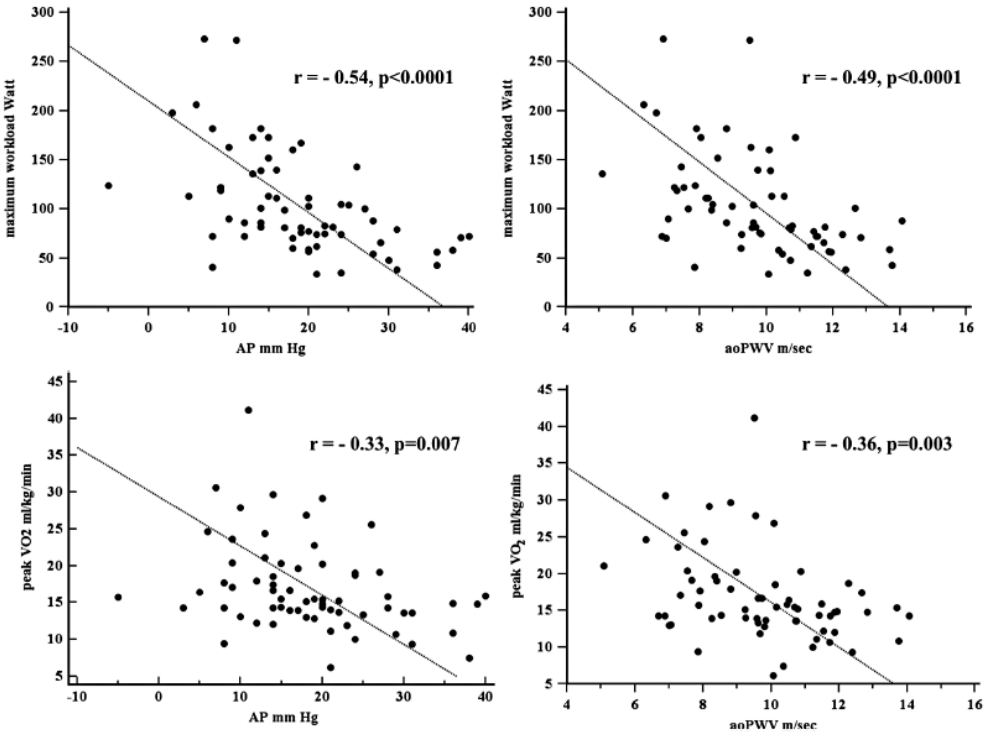

Figure 3. Reproduced from (1) **with permission of oxford university press.** Inverse relationship between exercise capacity (maximum workload—upper panel; peak VO_2—lower panel) and pulsatile hemodynamics (pressure augmentation [AP]—left side; aortic pulse wave velocity [aoPWV]—right side)

3. Multivariable models (multiple regression) to predict exercise capacity

3.1 Peak VO_2

In multiple regression models to predict peak VO_2, age, gender, BMI, E/E´, SV, log NT proBNP, HR at rest, presence of hypertension, presence of diabetes, and parameters of pulsatile hemodynamics were included. In addition to the parameters of pulsatile function, the following covariates were significantly associated with peak VO_2: BMI, age, E/E´, HR. (Table 21.) (1)

Table 21. Multivariate associations between peak VO_2 and measurements of pulsatile hemodynamics (1)

Parameter	Coeff	p-value	Coeff of determination R^2 full model
Tr ms	0.1650	0.001	0.64
AP mmHg	-0.1913	0.008	0.65
AIx75 %	-0.1557	0.03	0.63
AIx %	-0.1568	0.05	0.61
Pb mmHg	-0.203	0.03	0.62
Estimated aoPVW m/s	-1.02	0.003	0.66

3.2 Maximum workload

In multiple regression models to predict maximum workload, age, gender, BMI, E/E´, SV, log NT proBNP, HR at rest, presence of hypertension, presence of diabetes, and parameters of pulsatile hemodynamics were included. In addition to the parameters of pulsatile function, the following covariates were significantly associated with maximum workload: gender, age, HR. (Table 22.) (1)

Table 22. Multivariate associations between maximum workload and measurements of pulsatile hemodynamics (1)

Parameter	Coeff	p-value	Coeff of determination R^2 full model
Tr ms	0.7708	0.035	0.77
AP mmHg	-1.692	0.011	0.78
Pb mmHg	-1.7614	0.019	0.77
Pf mmHg	-1.233	0.02	0.77
aoPP mmHg	-0.7214	0.03	0.77
bPP mmHg	-0.6	0.051	0.76
Estimated aoPVW m/s	-10.0712	<0.0001	0.77

4. Pulsatile hemodynamics in patients with and without HFpEF

In 33 patients NT proBNP levels were elevated and in 20 patients E/E´ was elevated. 33 patients had left LVH and in 14 patients the LA was enlarged. (1) When we grouped patients according to recent guidelines (8), 32 were diagnosed with HFpEF. Importantly, exercise capacity of patients diagnosed with HFpEF was lower, as compared to controls: Maximum workload was 93.5 versus 117.3 watts (p=0.0006), and peak VO_2 was 16.2 versus 18.0 mL/min/kg (p=0.047) in patients with HFpEF versus controls, respectively. (1) Patients with HFpEF had higher brachial and central SBP, higher brachial and central PP, a higher amount of wave reflections, a trend towards a shorter Tr, and a higher estimated aoPWV, as compared to controls. (Table 23.) (1)

Table 23. Pulsatile hemodynamics in HFpEF patients and controls (1)

Parameter	HFpEF(32) Means (SD)	Control (32) * Means (SD)	p-value
HR min^{-1}	59 (8)	60(10)	0.83
bSBP mmHg	149(14)	137(15)	0.001
bDBP mmHg	82(8)	81(10)	0.75
bPP mmHg	67(13)	56(14)	0.001
cSBP mmHg	141(15)	128(13)	0.0004
cPP mmHg	58(13)	45(12)	0.0002
AP mmHg	22(9)	15(8)	0.002
AIx %	37(11)	32(13)	0.14
AIx75 %	29(9)	25(11)	0.13
Pf mmHg	36(8)	29(8)	0.001
Pb mmHg	24(6)	19(5)	0.0001
Tr ms	130(13)	135(10)	0.06
Estimated aoPVW m/s	10.9(1.6)	8.5(1.6)	<0.000006
*** not all parameters under consideration were available in all patients**			

IV DISCUSSION

Heart function is necessarily linked to the function of the arterial system. The arteries serve as a conduit and cushion between the heart (which propels the blood) and the

microcirculation. (212) Measurement of brachial SBP and DBP is performed everyday in clinical routine. Its value in understanding the complex interaction between the heart (the pump) and the arterial circulation is limited. For a better understanding, BP should be seen as a curve, rather than two points (SBP, DBP), with a defined amount of pressure (PP) fluctuating around a mean value (MAP); the characteristics of the curve allow insights into arterial function. (213) Another aspect is the fact that BP originates from the interplay between cardiac and arterial function. BP is the product of the pressure and flow generated by the heart and the afterload imposed by the arterial tree. Patients with identical BPs may have substantially different afterload patterns due to differences in the blood flow generated by the left ventricle. (213) In general, due to increased arterial stiffening and increasing wave reflections with age, the influence of arterial properties on left ventricular load increases with age. This increase in arterial stiffness is referred to as arteriosclerosis and is mainly a disease of the arterial media, which is different from atherosclerosis (plaque), which is initially and mainly a disease of the arterial intima. (214) The pressure wave (pulse wave), produced by the heart with every heart beat, travels faster (with a higher velocity) in a rigid tube, leading to a higher PWV with stiffer arteries. (214) This makes an increased PVW a hallmark of increased arterial stiffness. (214) This loss of compliance in arterial walls, affects especially elastic type arteries like the aorta. (214) In addition, the pulse wave generated with every heart beat, is reflected at myriads of sites of impedance mismatch in the arterial system (most likely, the major reflection sites are located at the level of the arterioles). The reflected waves travel back to the heart, with the same speed (PWV) as the forward wave, and merge with the incident wave (the one produced by the heart) within the same cardiac cycle. (215) In young individuals with low PWV, antegrade and reflected waves merge in diastole, increasing DBP and boosting coronary perfusion (which occurs mainly in diastole). In old individuals, PWV increases, and reflected waves merge with antegrade waves in systole, which increases systolic load to the heart, and may compromise coronary perfusion. (216)

The most widely used and validated techniques of quantifying pulsatile hemodynamic parameters are measurements of arterial stiffness and wave reflections. They are emerging as promising biomarkers. (223) Therefore, ESC guidelines give Class IIa/A and IIb/B recommendations for PWV and wave reflections accordingly regarding usefulness for primary and secondary CV disease prevention. (160) bPP, a crude estimate of arterial stiffness, can be easily obtained with a simple BP cuff by subtracting DBP from SBP. A

bPP >60 mmHg indicates large artery organ damage according to the latest European Society of Hypertension / European Society of Cardiology Guidelines on Hypertension. (159) PP increases with stiffening of the aorta and the large arteries and decreases with severely impaired systolic LVF. In populations, PP increases with aging, particularly after the age of 55 years. (217) It is closer related to cardiovascular risk in middle aged and elderly individuals than other BP components. However, PP depends on cardiac function, which leads to a "paradoxical" inverse relationship with cardiovascular events and mortality in patients with severely impaired systolic function. Therefore, more specific measurements of arterial stiffness are desirable. Central (aortic) PP (cPP) is closer related to organ damage and prognosis, (214) but its measurement is more complex and involves assessment of waveforms, their calibration and algorithms (mostly transfer functions) to derive central waveforms. Wave reflections can be quantified from central waveforms alone, using the technique of PWA as mentioned earlier (215): an early systolic shoulder is identified mathematically on the contour of the pulse wave, which corresponds exclusively with the forward wave (P1). The following inflection point is due to the merging of the forward wave with the incoming reflected wave, and the second systolic peak (P2) is due to the maximum effect of the reflected wave on the central pressure contour. Wave reflection thus can be quantified by (P2-P1) called AP. This is often related to PP (AP/PP) called AIx. However, the pulse contour (and the derived measurements AIx and AP) depends not only on the magnitude, but also on the timing of wave reflection in relation to the duration of left ventricular systole (which is determined among others by heart rate and systolic function). To overcome this potential shortcoming, WSA (181) has been developed, using simultaneously acquired pressure and flow waves to separate the pressure wave into its forward (Pf) and backward (Pb) components. In addition, the ratio Pb/Pf is calculated (RM). Whereas pressure waves can be easily recorded, it is inconvenient (or nearly impossible) in clinical routine to record flow waves simultaneously. As a substitute, triangular, averaged, or model derived flow waveforms (184) have been developed and validated. PWV as a measure of regional arterial stiffness is a relatively simple, robust procedure. (213) Currently it is recommended that the aorta is included in the arterial pathway (as with cfPWV), because a large number of studies consistently has shown its independent prognostic value. Therefore, cfPWV has been recommended as a measure of subclinical organ damage in the latest European Society of Hypertension/European Society of Cardiology Guidelines on Hypertension. (159) Based on available data, and a consensus regarding the measurement details, a cutoff value of 10 m/s has been proposed. (159)

However, measurement of cfPWV in clinical routine is inconvenient and time consuming and therefore rarely performed. As an alternative, estimates of aoPWV, based on single site recording and analysis of brachial waveforms (obtained with a cuff) have been developed and validated. (210)

In many studies they have been shown to be independent predictors of CV mortality and events in populations of acute heart failure (224), patients undergoing coronary angiography (176) or interventions (225), patients with impaired renal function (226) or dialysis patients (181). Also in a meta analysis of 5648 individuals it could be shown that pulsatile hemodynamics like cSBP, cPP and AIx were independent predictors of CV events. (218) Moreover, AIx even predicted all cause mortality expanding its role beyond the CV system. (218) central PP showed a better predictive ability for clinical events compared to peripheral PP. (218)

In the pathogenesis of HFpEF increased arterial stiffness is involved through direct [abnormal relaxation in DHF (219)) and indirect (LV hypertrophy (220)(221)(222)(223) and LA enlargement (12)] mechanisms.

LVH is a classical marker of organ damage in hypertension and an intermediate step from hypertension to HF. (159) LV mass is closer related to PP than to MAP, showing the importance of pulsatile hemodynamics. This relationship is stronger for cPP, in particular when measured over 24 hours. (224) Reductions in LV mass, which have prognostic benefit, are more closely associated with reductions in wave reflection than with reductions in BP. (225)

The relationship between late systolic load and diastolic function of the LV has been studied in animal experiments. The time of onset of diastole (226) and the duration of relaxation (227) depends on systolic load. In dogs, the influence of the systolic LV pressure waveform on the rate of diastolic function (isovolumetric LV pressure fall, assessed by the time constant tau), was examined. (228) Inflating an intra aortic balloon led to increases in LV pressure of 2-20 mmHg, which in termed to a prolongation of tau. Importantly, the rate of LV pressure fall slowed significantly more when LV pressure was increased in late than in early systole. The authors explained the findings with delayed cross bridge inactivation due to late systolic loads. Similar results could be obtained in patients during heart catheterization: (219) Compression of both femoral arteries led to a measurable increase of wave reflection in these patients. (219) In younger patients, the

reflected wave arrived at the ascending aorta after aortic valve closure, and relaxation shortened. (219) In contrast, in elderly patients, the increased reflected wave arrived in late systole, and relaxation was prolonged. (219) Taken together, these observations suggest that late systole is a vulnerable period of the cardiac cycle, and that increased load in late systole (increased PP, increased and premature wave reflections) may lead to diastolic dysfunction and, in the long term, to HF in humans. (219)

Indeed, increased arterial stiffness (PWV) and wave reflections (AIx, AIx75, AP) were associated with higher filling pressures, measured invasively (LVEDP). (9) The same was shown for the association with noninvasively estimated filling pressures (E/E′). (9)This was shown also in another study (10), where measures of arterial hemodynamics complemented echocardiographic imaging in patients with unexplained exertional dyspnoea in stable, non-decompensated patients. The authors based the diagnosis of HFpEF patients on invasively derived LV filling pressures with cut off values according to accepted guidelines (29) in combination with plasma levels of natriuretic peptides (29). By following this strategy they were able to investigate the diagnostic performance of pulsatile hemodynamics independently of echocardiographic measures and to compare pulsatile hemodynamics and echocardiography against each other and in combination. (10) Furthermore pulsatile hemodynamics have been shown to be elevated in diastolic dysfunction. (9)(188) A series of studies confirmed the association between diastolic dysfunction/HF and increased PWV/increased central pressures. (154)(189)(190)(191) HFpEF patients had increased central aortic stiffness (cfPWV, forward wave amplitude) relative to age matched healthy and hypertensive subjects without HF. (189) cfPWV appeared to be superior to central and brachial PP for the detection of diastolic dysfunction in older adults with HFpEF. (229) The relation to parameters reflecting cardiac diastolic dysfunction could be also shown for brachial ankle PWV. (190)(191)

Arterial wave reflections were shown to be an important novel risk factor for CHF. (186) Longitidinal studies support this point of view: In the Framingham study, bPP (and bSBP) were stronger predictors than DBP for congestive HF. (67)(160) RM as a parameter of wave reflections predicted the occurrence of HF and severe CV events in a large multiethnic study. (230) In the MESA (Multiethnic Study of Atherosclerosis) study, RM was strongly and independently predictive of new onset HF, even in patients with normal BP. In the Framingham Heart study (231), after adjustments for standard risk factors including MAP, cfPWV was associated with both HFpEF and HFrEF. In 2602 patients

with chronic moderate renal impairment (mean GFR 45 ml/min/1.73m^2), cfPWV showed the best relationship with hospitalized HF. (232) In asymptomatic patients at risk for HF, worsening of arterial stiffness (increase in baPWV) within 5 years was associated with increased risk of incident HF. (233)

The studies cited above have shown the relationship between measures of pulsatile hemodynamics and structural or functional cardiac changes or the development of HF. However, from a patient´s perspective, limitations of everyday activities due to impairment in exercise capacity is of high importance. Therefore, the main interest of the current study was to investigate the interplay between exercise capacity and pulsatile hemodynamics. Only very few studies have investigated this topic so far. In other words, our study aimed to extend previous results on measurements of cardiac dysfunction to objective evidence of exercise impairment.

We included 66 patients with exertional dyspnea in our study group. Exclusion criteria were a pulmonary cause of dyspnea, a reduced EF, valvular disease, as well as atrial fibrillation. CAD was present in 10%, a significant coronary obstruction at the time of presentation was ruled out by angiography as to rule out this as a cause of dyspnea. Mean Hb was 14.1 g/dL ruling out anemia as a cause of dyspnea as well. 65% of the patients were women, which correlates with current bibliography regarding HFpEF patients as being more often female. (22) 84% had hypertension being in accordance to that beeing the leading cause of HFpEF. (25) EF measured invasively and non invasively was normal as it should be in HFpEF. Mean bBP was mildly elevated (144/82 mmHg) under antihypertensive treatment. Mean bPP was 62 mmHg (values >60 being indicative of risk for HF in asymptomatic patients).

When comparing the results according to sex we could find that pulsatile hemodynamics as AP, AIx, AIx 75, Pb, RM were higher in women than in men as they are the more prevalent group of having HFpEF. It is also partially related to the shorter body height in women allowing earlier arrival of the reflected waves.

Exercise capacity indicated by peak VO_2 and maximum workload was higher in men than in women due to higher muscle mass.

When comparing our group to an 8 years younger population with chronic DHF (234) we could see, that our patients had a lower exercise capacity indicated by peak VO_2 (16.2 mL/kg/min vs 18.4 mL/kg/min). This implies true functional limitation in our patients. (1)

We grouped our patients according to the recent guidelines for HFpEF. We could diagnose 32 for having HFpEF. Exercise capacity of patients diagnosed with HFpEF was lower, as compared to controls: Maximum workload was 93.5 versus 117.3 watts (p=0.0006), and peak VO_2 was 16.2 versus 18.0 mL/min/kg (p=0.047). Patients with HFpEF had higher brachial and central SBP, higher brachial and central PP, higher wave reflections and a higher estimated aoPWV.

We compared peak VO_2 of our two groups to values by another study, (235) that compared peak VO_2 in roughly 70 year old individuals with HFpEF and healthy adults. They observed values of 14.1 mL/kg/min and 19.7 mL/kg/min respectively. These results are placing our two groups (peak VO_2 16.2 and 18.0 mL/kg/min in HFpEF and no HFpEF individuals) in between. (1)

As expected, age, NT proBNP and BMI were inversely associated to exercise capacity. This makes sense as the older and heavier somebody is the worse is going to be his exercise performance. The worse the heart failure the worst the exercise performance. In contrast body height was directly associated with exercise capacity. E/E´ was inversely associated with exercise capacity and as somebody would expect, measures of wave reflections and estimated aoPWV were inversely related to most measures of exercise capacity. (1)

Accordingly, we observed an independent relationship in our patients between several measurements of exercise capacity and pulsatile hemodynamics at rest. (1) In other words, an impairment in exercise capacity was associated with worse pulsatile function. The current study extends previous results (9)(188) of a relationship between resting measures of diastolic function and measures of pulsatile arterial function to an objective assessment of exercise capacity. A recent cross sectional study (RELAX) also hypothesized that measures of resting LV diastolic function, myocardial contractility and vascular function would be associated with peak VO_2 in HFpEF independently of age, sex and body size. (48) Age, sex, BMI, Hb and chronotropic reserve collectively explained 64% of the variability in peak VO_2. After accounting for these variables, LV size and mass, parameters reflecting the severity of diastolic dysfunction and elevated LV filling pressures, SV, and

systemic arterial function were each only modestly associated with peak VO_2. (48) In contrast to our study they did not take into count parameters of pulsatile hemodynamics as derived from Sphygmocor usage and they only correlated the diastolic function parameters to the VO_2 as a surrogate of exercise capacity. In our study we also took into account other parameters indicative of arterial stiffness that lead to impairment of exercise capacity. For pulsatile hemodynamics as AIx, AIx75, AP and Tr time we found a corretation with peak VO_2 allowing the validation of our hypothesis. (1) When taking into account other parameters of exercise capacity as maximum workload we could show a correlation to other parameters of the PWA. (1) In contrast to them we found a statistically significant correlation of E/E´ to peak VO_2. This might be due to the fact, that they included just patients with expected VO_2max <60%, indicating severe exercise intolerance in contrary to our patient group where this was no inclusion criteria. Our group reached a mean peak VO_2 expected of over 80%, meaning that the exercise intolerance in total was not dramatically reduced. (1)

There have been other studies examining the correlation between measures of arterial stiffness and cardiorespiratory fitness as well in the past. The study group of those studies included athletes and healthy subjects, (236)(237) patients with coronary heart disease (CHD) undergoing rehabilitation, (235) and patients with DHF (192)(238) and HFrEF. (239) Our findings are consistent with theirs. Those studies focused however on univariate correlations and differences between healthy and diseased groups. There have been no multivariable models, including contemporary echocardiographic parameters (E/E´). Ours was the first to combine those parameters, giving a stronger impact on that topic. In our multiple regression analysis models to predict exercise capacity (as indicated by and maximum workload) age, gender, BMI, E/E´, SV, log NT proBNP, HR at rest, presence of hypertension, presence of diabetes, and parameters of pulsatile hemodynamics were included. AP and estimated aoPVW were significantly associated with both parameters of exercise capacity, whereas AIx, AIx 75 were associated with the primarily parameter of exercise capacity peak VO_2. In addition to the parameters of pulsatile function BMI, age and E/E´ where the covariates significantly associated with peak VO_2. (1)

There is an association between aging and stiffening of the large conduit arteries, accelerated by different cardiovascular risk factors, particularly by hypertension. (63) Accordingly, there is a close relationship of all parameters of pulsatile arterial function to aging. (169) Therefore, the European Society of Hypertension included elevated aortic

stiffness in the list of target organ damages to be screened for in hypertension. (160) Interestingly, in our multivariable models, parameters of pulsatile arterial function, but not chronological age itself remained significantly associated with peak VO_2 after adjustments. (1) This may suggest that biological or vascular aging rather than chronological aging is the important one in effecting exercise capacity through impaired pulsatile hemodynamics.

The limitation of our study was that not all patients accounted for exertional dyspnoea fulfilled all the criteria of the recent HF guidelines. (8) The relationship however between measures of pulsatile hemodynamics and exercise capacity is continuous rather than categorical, as can be seen easily on Figure 2. (1) Guidelines, on the other hand, need to rely on categories for reasons of simplification, and recommendation for diagnosis and treatment management. (1) Furthermore, as our study is of observational character, it does not allow firm conclusions about causality. Nevertheless, a bidirectional relationship is plausible: exercise capacity may be impaired due to increased pulsatile afterload (our main hypothesis). (1) On the other hand, pulsatile hemodynamics (as well as exercise capacity) can be improved with regular exercise, as we (235) and others (240)(241)(242) have shown previously. In term, a higher exercise capacity will be associated with "better" pulsatile hemodynamics.

An interesting future implementation will be, whether there is going to be a pharmacological treatment method for improving pulsatile hemodynamics and exercise capacity. Focus has been given until now to PVW and BP improvement by antihypertensive drugs.

As mentioned higher BP leads to dilatation of the arteries, explained by the interplay between elastin and collagen fibers in the vessel media. (140) This results in stiffening of the arteries with higher PVW, yet without any change in the properties of the arterial wall itself. (140) On the other hand, arterial stiffening describes structural changes in the intrinsic properties of the vessel wall. (140) The same pressure leads to a higher PWV. Accordingly, in a stiffer artery compared to a more elastic one, PWV is elevated beyond the effect of BP. (140) Elevated stiffness leads to an increase in BP, being further indirectly augmented by the earlier return of the reflected waves due to the faster PWV. (140) The relationship between BP and PWV is bidirectional as both variables are mutually influencing the progression of each other. (140) Increased BP is causing increased cyclic stress on the arterial wall. This is supposed to accelerate vascular

degradation (mechanical fatiguing). (140) On the other hand, an association between elevated cfPWV and new onset hypertension with progressive rise of SBP in normotensive individuals was shown by Kaess and co (243) Therefore, due to this bidirectional relationship an improvement in one of them will lead to an improvement of the other. Antihypertensive medication effects on arterial stiffness depend on the drug class and the treatment duration. (244)(245) The meta analysis by Ong et al. (244) showed a short term lowering of cfPWV beyond BP for ACE inhibitors only, whereas in long term treatment (1–6 months), also for calcium channel blockers, beta blockers as well as diuretics. This could be explained by possible reverse remodelling of the arterial wall when BP is controlled and the load on the arterial wall reduced. (244) Numerically the highest reduction of cfPWV was shown by ACE inhibitors in long term treatment. (244) In contrary, in another meta analysis including 9 trials and 378 patients, the superiority of ACE inhibitors compared to other antihypertensive drug classes could not be confirmed. (246) This has been attributed to the lack of power and quality of the randomized controled studies included. (246) Ait Oufella et al. (245) also showed a progressive temporal reduction in cfPWV beyond BP in cfPWV in patients treated for hypertension according to routine clinical practice over an even longer period of 5.3 years. Therefore, further research is definitely needed to get clear results about methods of treatment of arterial stiffness. Focus should be given in future studies also to changes in other parameters of pulsatile hemodynamics by these treatments beyond PVW. The Conduit Artery Functional Evaluation (CAFE) study showed, that an improvement in wave reflections will lead to a reduction in CV events. (247) In that study, a calcium channel blocker seemed to be more effective than a beta blocker in lowering cSBP and reducing CV events, even though peripheral SBP reduction was similar with both medications. (247) There will be a need to find, if and how changes in pulsatile hemodynamics are going to affect exercise capacity. The methods of improvement in pulsatile hemodynamics and exercise capacity are going to be the subject for future studies.

In conclusion, pulsatile hemodynamics are indepedently associated not only with cardiac filling pressures and biochemical markers of HF at rest, as shown previously, but also with gold standard measurements of exercise capacity in patients with exertional dyspnea and heart failure with preserved ejection fraction. (1)

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APPENDIX

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