Diploma Thesis

The predictive value of non-invasive pulse wave analysis in chronic heart failure

submitted by

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Zusammenfassung

Hintergrund: Chronische Herzinsuffizienz (CHF) ist eine wesentliche Ursache für Morbidität und Mortalität. Bei CHF zeigen sich charakteristische Veränderungen der Pulswellen, deren prognostische Bedeutung jedoch unklar ist.

Methoden: In einer prospektiven Kohortenstudie untersuchten wir den prognostischen Wert der nicht-invasiven Pulswellenanalyse (PWA) und Pulswellengeschwindigkeit (PWV) bei 205 Personen mit CHF und einer linksventrikulären Ejektionsfraktion (LVEF) ≤50 %. Der kombinierte Endpunkt umfasste ungeplante Hospitalisierungen aufgrund von Herzinsuffizienz sowie die Gesamtmortalität. Alle Teilnehmenden erhielten eine standardisierte Messung mittels des SphygmoCor CvMS-Systems. Uni- und multivariate Cox-Regressionen wurden zur Analyse der Assoziationen mit dem Endpunkt verwendet.

Ergebnisse: PWA war bei 169 Teilnehmenden (22,5 % weiblich) möglich. Das mediane Alter betrug 66,5 Jahre (IQR 58,1–73,2), die mediane LVEF 35,6 % (30,7–43,0). Der mittlere Augmentationsindex (AIx) lag bei 29,3±10,2 %, der frequenzkorrigierte AIx (AIx@75) bei 24,2±9,7 %. Im medianen Beobachtungszeitraum von 5 Jahren (4,0–5,3) erreichten 63 Personen (37,3 %) den kombinierten Endpunkt. Niedrigere Werte von AIx und AIx@75 waren signifikant mit einem ungünstigen Verlauf assoziiert (HR 0,971 [0,947–0,996], p=0,023 bzw. HR 0,974 [0,949–1,000], p=0,049), auch nach Adjustierung für Alter, Geschlecht, Body Mass Index, Blutdruck, LVEF und Nierenfunktion (HR 0,958 [0,924–0,994], p=0,023 bzw. HR 0,962 [0,926–1,000], p=0,048). PWV-Messungen waren bei 78 Teilnehmenden möglich (Mittelwert 7,4±1,9 m/s). Diabetiker*innen (28,2 %) zeigten signifikant höhere PWV-Werte (8,3±2,0 vs. 7,0±1,8 m/s, p=0,004); auch bei Hypertonie (76,7 %) war die PWV tendenziell, jedoch nicht statistisch signifikant, erhöht (7,7±2,0 vs. 6,9±1,8 m/s, p=0,059). PWV war nicht mit dem Outcome assoziiert (HR 0,932 [0,762–1,141], p=0,496).

Schlussfolgerung: Ein niedriger AIx war, unabhängig von Konfoundern, mit einem ungünstigen Verlauf bei CHF assoziiert, was auf eine prognostische Relevanz der PWA in dieser Population hinweist. Die PWV war in unserer Kohorte nicht prädiktiv für das Outcome.

Abstract

Background: Chronic heart failure (CHF) remains a major cause of morbidity and mortality. Pulse waveforms are altered in CHF, but the prognostic value of these changes has not been fully established.

Methods: We investigated the prognostic significance of parameters derived from non-invasive pulse wave analysis (PWA) and pulse wave velocity (PWV) in CHF patients, with a composite endpoint of unplanned hospitalization for worsening heart failure and all-cause mortality. In a prospective, single-center cohort study, 205 patients with CHF and left ventricular ejection fraction (LVEF) ≤50% were enrolled. All participants underwent standardized PWA and PWV assessments using the SphygmoCor CvMS system. Univariate as well as multivariate Cox regression models were used to analyze associations with outcomes.

Results: PWA was feasible in 169 patients, 22.5% of whom were women. The median (interquartile range) age was 66.5 years (58.1–73.2), and median LVEF was 35.6% (30.7–43.0). Mean (±standard deviation) augmentation index (AIx) was 29.3±10.2%, and heart rate-corrected AIx (AIx@75) was 24.2±9.7%. Over a median follow-up of 5 years (4.0–5.3), the composite endpoint occurred in 63 patients (37.3%). Both lower AIx and AIx@75 were significantly associated with adverse outcomes in univariate analysis (HR 0.971 [0.947–0.996], p=0.023 and HR 0.974 [0.949–1.000], p=0.049, respectively), and remained significant in multivariable models adjusting for age, sex, body mass index, blood pressure, LVEF, and estimated glomerular filtration rate (HR 0.958 [0.924–0.994], p=0.023 and HR 0.962 [0.926–1.000], p=0.048).

PWV measurements were feasible in 78 patients. Median PWV was 7.4±1.9 m/s. Diabetic patients (28.2%) had significantly higher PWV (8.3±2.0 vs. 7.0±1.8 m/s, p=0.004); PWV was also higher in hypertensive patients (76.7%), though not statistically significant (7.7±2.0 vs. 6.9±1.8 m/s, p=0.059). PWV was not predictive of the composite endpoint (HR 0.932 [0.762–1.141], p=0.496).

Conclusion: Lower AIx was independently associated with adverse outcome in CHF patients, suggesting a prognostic role of PWA in CHF.

PWV was not predictive of outcomes in our cohort.

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Abbreviations and Definitions

ACS	*Acute Coronary Syndrome*
AIx	*Augmentation Index*
AIx@75	*Augmentation Index adjusted to heart rate of 75 bpm*
BMI	*Body Mass Index*
BNP	*B-type Natriuretic Peptide*
bpm	*beats per minute*
CHF	*Chronic Heart Failure*
CI	*Confidence Interval*
CMP	*Cardiomyopathy*
DCM	*Dilated Cardiomyopathy*
DM	*Diabetes Mellitus*
ECG	*Electrocardiography*
eGFR	*estimated Glomerular Filtration Rate*
HF	*Heart Failure*
HFimpEF	*Heart Failure with Improved Ejection Fraction*
HFmrEF	*Heart Failure with Mildly Reduced Ejection Fraction*
HFpEF	*Heart Failure with Preserved Ejection Fraction*
HFrEF	*Heart Failure with Reduced Ejection Fraction*
HR	*Hazard Ratio*

ISCV	*IntelliSpace Cardiovascular*
KDIGO	*Kidney Disease: Improving Global Outcomes*
LVEF	*Left Ventricular Ejection Fraction*
mmHg	*millimeters of mercury*
m/s	*meters per second*
NT-proBNP	*N-terminal pro-brain natriuretic peptide*
NYHA	*New York Heart Association*
PLAX	*Parasternal Long Axis view*
PSAX	*Parasternal Short Axis view*
PWA	*Pulse Wave Analysis*
PWV	*Pulse Wave Velocity*
RoC-HF	*Role of Comorbidities in Chronic Heart Failure study*
2D	*Two-dimensional*
3D	*Three-dimensional*

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1. Introduction

1.1 Chronic Heart Failure

The European Society of Cardiology defines chronic heart failure (CHF) as a clinical syndrome characterized by key symptoms such as breathlessness, ankle swelling, and fatigue, often accompanied by signs like elevated jugular venous pressure, pulmonary crackles, and peripheral edema due to structural and/or functional cardiac abnormalities.[1] These symptoms often negatively impact functional capacity and quality of life. In about two-thirds of patients with left ventricular systolic dysfunction, the primary cause is coronary artery disease, also known as ischemic heart disease. In the remaining cases, left ventricular systolic dysfunction results from non-ischemic factors, which include a wide range of conditions. These include hypertension, valvular diseases, arrhythmias, cardiomyopathies, congenital heart disease, infectious causes, drug-induced damage, infiltrative and storage disorders, endomyocardial and pericardial diseases, as well as metabolic and neuromuscular abnormalities.[1,2]

1.1.1 Scope of the Problem

Heart failure poses a significant global health challenge, impacting around 64.3 million people across the globe.[3] The European Society of Cardiology, representing 56 countries, reported 15 million patients suffering from heart failure.[4,5] This concludes to a prevalence of approximately 1-2% of adults, although the actual prevalence is suspected to be even higher.[1] In Germany, health care data from over 3 million residents estimated the prevalence of heart failure at 4% for both men and women.[6] The incidence rate, regarding adults, lies at about 5/1000 persons per year.[1]

This trend is also observed in the United States, where it is estimated that by 2030, more than eight million people, approximately 1 in 33, will be affected by heart failure.[7]

Hospitalization due to heart failure remains a significant concern. In both Europe and the United States, heart failure is the leading cause of hospitalization, accounting for approximately 1 million admissions where it is the primary diagnosis.[5] This trend appears to be on the rise, as a recent study in the United Kingdom revealed. Analyzing hospitalization rates in heart failure patients, the study found a 28% increase in age-adjusted incidence for both heart failure-related and all-cause admissions.[8] In Austria a report from the Federal Ministry of Health in 2019 examined hospitalizations for all cardiovascular diseases, including cerebrovascular conditions. Notably, heart failure was the primary diagnosis in 46 853 hospitalizations that year.[9]

The significant morbidity and frequent hospitalizations associated with heart failure result in a notable economic burden. In terms of prognosis, patients with CHF show high mortality rates. A trial conducted in Minnesota found the mortality rate at a five-year follow-up to be 24.4% for 60-year-olds and 54.4% for those aged 80.[10] A pooled analysis of the Framingham Heart Study and the Cardiovascular Health Study looking at the incidence and mortality of heart failure and its subtypes determined an even worse prognosis: the analysis comprised 2 524 cases of heart failure, aged above 60 years, and reported a mortality rate of 67.4% within five years after diagnosis.[11]

1.1.2 Classification by Ejection Fraction

CHF is currently classified based on left ventricular ejection fraction (LVEF). While this classification provides useful therapeutic guidance, it also has limitations, as echocardiographic measurements may vary between individuals. Heart failure is commonly divided into four subtypes:

Heart Failure with Reduced Ejection Fraction (HFrEF) is defined by an LVEF of 40% or less. Patients in this category generally have a worse prognosis but also benefit most clearly from established guideline-directed medical therapies.

Heart Failure with Preserved Ejection Fraction (HFpEF) includes patients with an LVEF of 50% or more who present with typical symptoms of heart failure along with structural or functional cardiac abnormalities. Elevated natriuretic peptides often support the diagnosis in these patients.[1]

The term Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF) is used for patients with an LVEF between 41 and 49%. Retrospective analyses of randomized controlled trials suggest that these patients may benefit from therapies similar to those used in HFrEF, although evidence is somewhat less robust.[1]

Finally, Heart Failure with Improved Ejection Fraction (HFimpEF) refers to patients who initially had HFrEF (LVEF ≤40%) and who, during therapy, exhibit a ≥10-point increase in LVEF to a value >40%. This favorable remodeling is thought to reflect a beneficial treatment response and may influence long-term prognosis.[12]

1.1.3 Diagnostic Tools and Diagnosis

1.1.3.1 Signs and Symptoms

Heart failure is a clinical syndrome with typical symptoms such as breathlessness, ankle swelling, and fatigue. Common signs include elevated jugular venous pressure, pulmonary crackles, and peripheral edema. These findings result from structural or functional cardiac abnormalities that reduce cardiac output or increase intracardiac pressures, either at rest or during stress. While these signs and symptoms suggest heart failure, they are not specific and must be interpreted in the overall clinical context.[1]

For a feasible classification of the functional limitations caused by heart failure, the New York Heart Association (NYHA) classification is commonly used. It assesses severity based on symptoms and their impact on daily activities.[2]

1.1.3.2 Natriuretic Peptides

B-type natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are secreted by the heart's ventricles. Within cardiomyocytes, the precursor protein proBNP is fragmented, resulting in the release of biologically active BNP and inactive NT-proBNP into the bloodstream. Left ventricular end-diastolic wall stress is the main trigger for BNP release. This stress is primarily caused by elevated left ventricular end-diastolic pressure due to volume overload or increased filling pressures. This means BNP levels reflect the extent of myocardial wall stress, which is seen in both systolic and diastolic heart failure.[13]

NT-proBNP and BNP levels are used for diagnosis of heart failure, but also for risk stratification following recent cardiac decompensation or acute coronary events. Furthermore, they are utilized for monitoring and adjusting treatment in CHF. They are also useful for screening individuals at risk of significant cardiac impairment.[14,15]

The European society of Cardiology established the upper limits of normal values in non-acute settings at 35 pg/mL for BNP and 125 pg/mL for NT-proBNP. Levels below these thresholds indicate a low probability of heart failure.[1]
However, it is essential to recognize that several conditions can lead to elevated levels of natriuretic peptides. These include atrial fibrillation, advanced age, and kidney disease. In patients with obesity, natriuretic peptide concentrations may be inadequately reduced, as adipose tissue contributes to enhanced peptide clearance and enzymatic degradation.[1]

1.1.3.3 Electrocardiography

Electrocardiography is a widely used diagnostic tool, particularly in cases where symptoms are nonspecific and access to advanced imaging modalities, such as echocardiography, is delayed. Systolic dysfunction of the left ventricle can lead to electrocardiographic abnormalities. However, subtle alterations can be easily overlooked or may lack specificity.[1,16]

1.1.3.4 Echocardiography

Transthoracic echocardiography is widely used in heart failure management due to its high feasibility, sensitivity, and specificity. It is considered the gold standard for assessing heart failure. Echocardiography allows for quick evaluations in nearly every clinical scenario, providing critical insights into the structure and function of all four cardiac chambers. It offers information on ventricular performance, LVEF, chamber volumes, wall thickness, and valve function. LVEF, as mentioned before, is a critical prognostic marker in CHF, as a reduced LVEF is associated with worse prognosis. By enabling the classification of LVEF, echocardiography plays an essential role in stratifying patients based on the severity of their condition, guiding therapeutic decision-making, and improving risk prediction. The use of echocardiography for evaluation and therapeutic guidance has been associated with a significant reduction in mortality.[1,17,18]

This underlines the importance of identifying and utilizing robust prognostic markers to enhance risk assessment and optimize patient outcomes in heart failure management.

1.2 Pulse Wave Analysis

1.2.1 The Concept of Pulse Wave Analysis and Velocity

Pulse wave analysis (PWA) and pulse wave velocity (PWV) are techniques used to investigate arterial function and the cardiovascular system. PWA uses mathematical algorithms to analyze the arterial blood pressure waveform. This waveform is determined by the interplay between cardiac ejection and the condition of the arterial system. Important influencing factors are aortic compliance, peripheral vascular resistance, and wave reflections. All of these provide insights into central hemodynamics. Important parameters derived from PWA are pulse pressure and the augmentation index (AIx). These PWA parameters can provide essential insights into central hemodynamics and can be useful for identifying early signs of cardiovascular dysfunction.[19,20]

PWV, on the other hand, is the gold standard for measuring arterial stiffness. It is defined as the velocity at which the pressure wave moves through the arterial system. PWV is calculated as the distance between two arterial sites divided by the time the pressure wave needs to travel. The pressure wave moves faster in stiffer arteries, therefore resulting in higher PWV values. Clinically higher values are associated with atherosclerosis, strokes and further cardiovascular diseases. Therefore, PWV is viewed as a valuable tool for risk stratification in both healthy individuals and patients with cardiovascular conditions.[21,22]

In recent years PWA and PWV have become increasingly popular for obtaining essential insights about the cardiovascular system. While PWA focuses on central blood pressures and wave reflections, PWV is able to detect advanced stiffness of large arteries. This information may be used to monitor disease progression and guide therapeutic interventions.[23,24]

1.2.2 Non-invasive Pulse Wave Analysis

Radial artery applanation tonometry, a common non-invasive method, uses a mechanical sensor on the skin to slightly compress the artery. This allows continuous blood pressure recording. Potential interfering factors are sensor displacement or patient movement, which can reduce signal quality and reliability. Still, the ability to continuously record the waveform without the need for arterial or venous access is a substantial advantage of non-invasive PWA. This makes the method both accessible and safe.[24]

Besides applanation tonometry, other non-invasive techniques for pulse wave analysis are oscillometric devices, for example. They use upper-arm blood pressure cuffs to estimate central pressures and arterial stiffness during normal inflation and deflation cycles. These systems are simple to use and common in clinical practice, though they provide less detailed waveform data.[25]

Another approach is the finger cuff method, which uses a small inflatable cuff to continuously record the blood pressure wave. This allows beat-to-beat monitoring and is based on keeping the finger artery at a constant volume.[26]

1.2.3 PWA Resulting Parameters

1.2.3.1 Pulse Pressure

Pulse pressure is best understood in the context of blood flow physiology. Blood flow is driven by the pressure difference between the two ends of a vessel and the resistance within the vessel. During systole, blood is ejected from the left ventricle into the aorta, where systolic arterial pressure is primarily determined by left ventricular stroke volume and aortic compliance. Diastolic arterial pressure, on the other hand, is influenced by left ventricular relaxation and systemic vascular resistance, which regulates peripheral blood flow. Pulse pressure is defined as the difference between systolic and diastolic arterial pressures. The mean arterial pressure represents the average pressure over one cardiac cycle.[27]

Mean arterial pressure can be considered the steady component of blood pressure, while pulse pressure represents the pulsatile component. At a given flow, the steady component (mean arterial pressure) reflects the status of small arteries, indicating total vascular resistance, compliance and tone. In contrast, pulse pressure is primarily influenced by two main factors: LVEF and aortic stiffness.[28,29]

An important physiological phenomenon is pulse pressure amplification. As the pulse wave moves along the arterial tree, pulse pressure increases, as schematically illustrated in Figure 1. This is primarily due to decreasing vascular compliance in distal arteries. Vascular compliance is defined as the ability of blood vessels to expand in response to pressure. It is physiologically higher in large central arteries compared to smaller peripheral vessels. Additionally, wave reflections augment the pulse wave while propagating, further increasing pulse pressure. However, pulse pressure amplification is largely a distortion of the pulse wave as mean arterial pressure alters only marginally.[30]

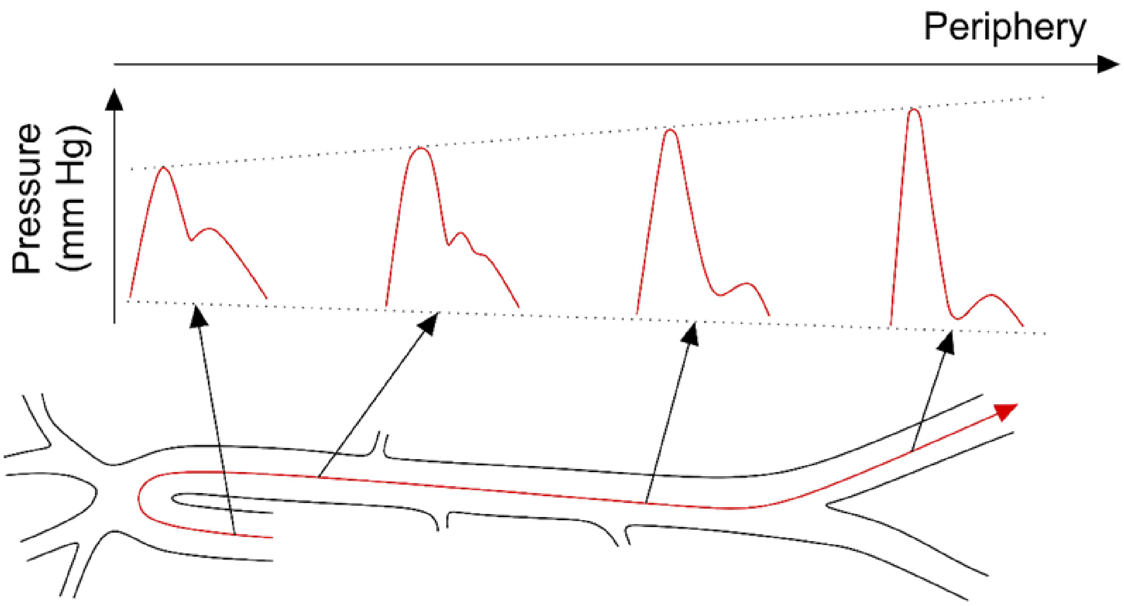

Figure 1: *Schematic illustration of pulse pressure amplification along the arterial tree from central to peripheral sites.*

Adapted from Saugel et al. Cardiac output estimation using pulse wave analysis: physiology, algorithms, and technologies. Br J Anaesth. 2021.[27]

1.2.3.2 Augmentation Pressure

Augmentation pressure is the increase in aortic systolic pressure due to reflected pressure waves returning to the central aorta. These waves originate from branches of peripheral arteries and contribute to the shape and amplification of the pressure waveform. Due to this, augmentation pressure is consistently higher in the aorta compared to more peripheral arteries.[31]

Augmentation pressure is measured by identifying the initial rise of pressure in the pulse waveform, which signifies the highest blood flow in the aorta. The measurement is taken from the first peak of the pressure waveform to the second peak during late systole. Augmentation pressure and pulse pressure within a single pulse wave are illustrated in Figure 2. However, accurately measuring augmentation can be challenging, especially when the initial rise occurs near the point where the reflected wave merges with the pressure waveform. Furthermore, the amplification of the pulse wave, as it travels from the ascending aorta to distal arteries, adds complexity to these measurements.[31]

Despite these challenges, the aortic pressure waveform can be reliably derived from the radial pressure waveform. This is because the properties of the upper limb arteries have been shown to be stable across different populations, including varying ages, blood pressure levels, and drug therapies. This allows for the use of a generalized transfer function. Therefore, non-invasive radial applanation tonometry is considered a reliable method for estimating aortic pressure values.[31]

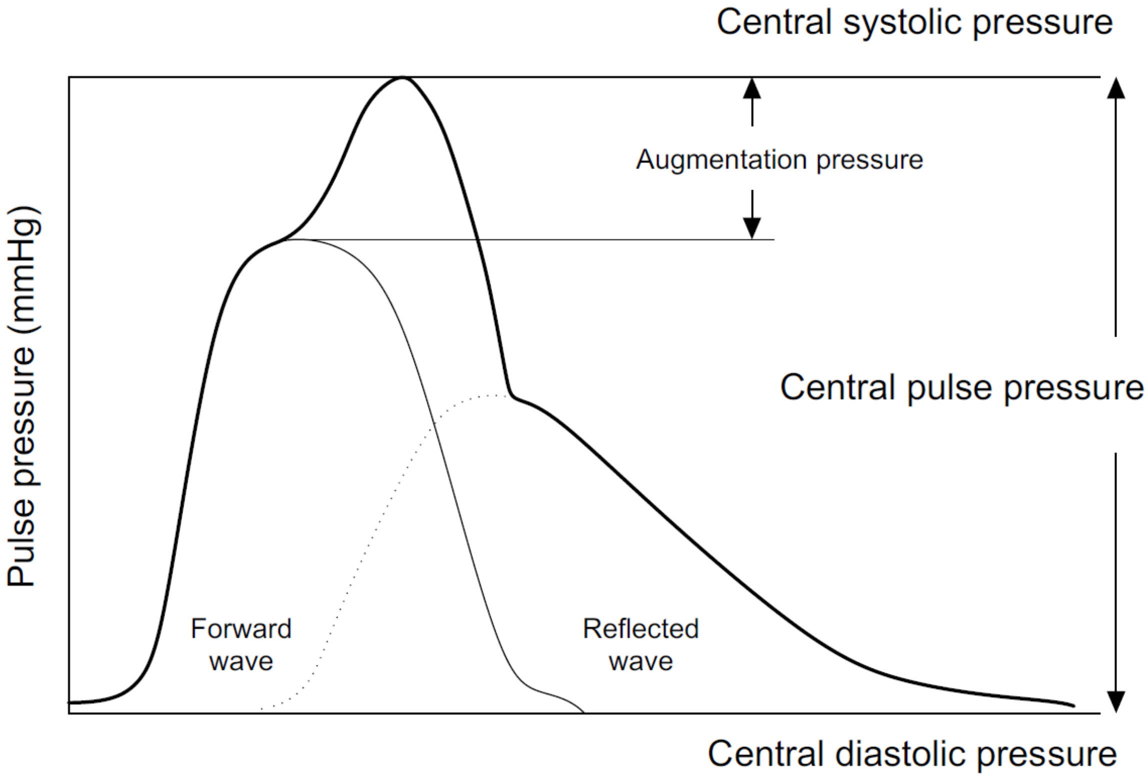

Figure 2: *Schematic illustration of the central pulse waveform showing forward and reflected wave, as well as key pressure components.*
Adapted from Parittotokkaporn et al. Carotid Pulse Wave Analysis: Future Direction of Hemodynamic and Cardiovascular Risk Assessment. JMA J. 2021[32]

1.2.3.3 Augmentation Index

The augmentation index (AIx) is the ratio of augmentation pressure to pulse pressure. AIx can be derived from the pressure waveform. Traditionally it is used as an indirect measure of the amount of blood flow being reflected retrograde towards the heart. While wave reflections contribute to AIx, studies have shown that it is significantly determined by aortic reservoir function and the elasticity of large arteries. As a result, changes in reservoir function, rather than wave reflections, are the main factors that significantly alter the aortic pressure waveform with aging.[33]

Furthermore, AIx is significantly influenced by heart rate. At higher heart rates, peripheral systolic, diastolic, and mean arterial pressures increase significantly. Central systolic pressure remains largely unchanged, despite a notable rise in central diastolic pressure. This phenomenon may be attributed to changes in systolic duration, which alters the timing of wave reflection. In this context, a study found a significant inverse linear relationship between AIx and heart rate. AIx proved to decrease by approximately 4% for every 10 beats per minute (bpm) increase in heart rate.[34]

To account for this phenomenon, AIx can be adjusted to reflect its value at a heart rate of 75 bpm. This heart rate-adjusted measure is commonly referred to as AIx@75.[35]

1.2.3.4 Velocity

PWV is defined as the speed at which a pressure wave travels between two points in the arterial system. Pulse timing at key arterial sites can be assessed non-invasively using arterial tonometry or Doppler ultrasound. Arterial tonometry measures the pressure upstroke, while Doppler ultrasound detects the flow upstroke. The gold standard for the assessment of PWV is the carotid-femoral PWV, recording signals at the carotid and femoral arteries.[36]

PWV is closely linked to arterial stiffness, as demonstrated by two key equations: the Bramwell-Hill equation and the Moens-Korteweg equation. The Bramwell-Hill equation describes an inverse, nonlinear relationship between PWV and the compliance of the artery, which is its ability to expand and contract in response to pressure. For example, a twofold increase in PWV corresponds to a fourfold decrease in arterial compliance. This change can be observed in humans as they age from 20 to 70 years. The Moens-Korteweg equation illustrates that PWV depends on the stiffness of the arterial walls, wall thickness, and lumen diameter. Stiffer walls result in faster wave propagation. Therefore, PWV serves as a surrogate parameter for arterial stiffness. Essentially, the stiffer the artery, the faster the pulse wave travels.[36]

The relevance of arterial stiffness lies in its significant impact on various organs. Especially the heart, brain, and kidneys are vulnerable to its effects. The heart is particularly impacted because a stiff aorta increases the pulsatile load on the left ventricle, requiring more effort to sustain sufficient cardiac output. This increased load is primarily due to heightened arterial impedance, which represents the resistance to blood flow. Heightened impedance results in elevated pressure waveforms and increased pulse pressure. As arterial stiffness rises, PWV increases as well, causing reflected waves to return earlier during systole. The reflected waves augment systolic pressure and increase the load on the left ventricle. Consequently, this heightened systolic pressure contributes to increased ventricular wall stress, concentric left ventricle remodeling, and hypertrophy. These mechanisms ultimately raise the risk of heart failure and atrial fibrillation. Regarding the brain and kidneys, aortic stiffening increases pulsatile power, allowing it to penetrate deeper into their microcirculation, potentially causing microvascular damage.[37–39]

1.2.4 Pulse Wave Analysis in Heart Failure

1.2.4.1 PWA in Heart Failure with Preserved Ejection Fraction

HFpEF is characterized by diastolic dysfunction, increased ventricular stiffness, and elevated filling pressures despite a normal LVEF. A key pathophysiological feature of HFpEF is increased arterial stiffness. It contributes to impaired adaptation of the heart to blood vessel stiffness and increased left ventricular afterload. Promoting factors for arterial stiffness are aging, endothelial dysfunction, hypertension, and comorbidities such as diabetes mellitus and obesity.[40]

In patients with HFpEF, PWA can provide insights into wave reflections and arterial stiffness. Increased wave reflections lead to a late systolic augmentation in the central pressure waveform, which can be recorded by PWA. This late systolic pressure peak imposes a greater load on the left ventricle and may further impair diastolic relaxation. For instance, elevated AIx has been associated with worsening diastolic function and increased filling pressures in HFpEF patients.[41–43]

1.2.4.2 PWA in Heart Failure with Reduced Ejection Fraction

HFrEF is primarily characterized by systolic dysfunction, leading to a progressive decline in cardiac output. Unlike HFpEF, arterial stiffness is often less pronounced in advanced HFrEF. This is due to lower mean arterial pressure and reduced pulsatile load. Even though hypertension is a major risk factor for the development of HFrEF, blood pressure often decreases as heart failure progresses due to hemodynamic deterioration and reduced cardiac output.[44,45]

Due to these hemodynamic changes, PWA plays a different role in HFrEF compared to HFpEF. Decreased left ventricular contractility results in reduced pulsatile energy transmission into the arterial system. As a result, lower pulse pressure and reduced AIx are commonly observed in these patients. While pulse pressure is in general considered an indicator of arterial stiffness, in HFrEF it primarily reflects left ventricular function rather than vascular properties.

Heart failure distinction is important when interpreting PWA findings, as the prognostic value of pulse pressure in HFrEF appears to be more closely linked to cardiac performance rather than arterial stiffness.[28,45–47]

1.2.5 Pulse Wave Velocity in Heart Failure

Elevated PWV values can be observed in both HFpEF and HFrEF patients, highlighting the role of arterial stiffness in heart failure pathophysiology. This is because PWV primarily reflects vascular properties and the stiffness of large arteries rather than direct cardiac performance. Increased arterial stiffness leads to higher left ventricular afterload, playing a key role in the pathophysiology and development of both HFpEF and HFrEF.

In HFpEF, elevated PWV is often linked to impaired diastolic function. In HFrEF, it can result from both vascular stiffening and reduced left ventricular contractility. Studies have shown that heart failure patients with increased PWV values face worse clinical outcomes. Therefore, assessing PWV in heart failure patients may provide valuable prognostic information and help guide risk stratification.[28,48]

1.3 Gaps in Evidence

While PWA and PWV show great potential in heart failure, their interpretation remains inconsistent across heart failure subtypes. Particularly in HFrEF, the evaluation of PWA parameters such as AIx and pulse pressure are challenging due to altered hemodynamics from reduced left ventricular function.

While elevated arterial stiffness is associated with worse outcomes, it is yet to be determined whether PWA provides prognostic information beyond established parameters such as age, gender, LVEF, systolic blood pressure, BMI and eGFR. The prognostic value of PWA in heart failure remains an active area of investigation.

1.4 Aim of the Thesis

The aim of this thesis is to thoroughly investigate whether PWA and PWV can provide meaningful prognostic insights into the outcomes of clinically stable patients with chronic HFrEF.

2. Methods

Data was obtained from the Role of Comorbidities in Chronic Heart Failure (RoC-HF) study, conducted from 2016 to 2018 at the Division of Cardiology at the Medical University of Graz (ClinicalTrials.gov Identifier: NCT02922478).

2.1 Study Overview and Study Population

The Roc-HF study is a longitudinal, prospective, single-center, epidemiological cohort study. Approval of the study was granted by the Ethics Committee of the Medical University of Graz (28-467ex15/16). A total of 205 participants were recruited directly from the department of cardiology.

The inclusion criteria for the study were: age ≥ 18 years, exertional dyspnea equivalent to NYHA class II to IV, a previous diagnosis of HFrEF, defined LVEF < 40% requiring optimization of therapy, an LVEF of less than 50% at the first visit, and guideline directed treatment according to the 2016 Heart Failure Guidelines from the European Society of Cardiology.[49] All participants provided signed informed consent before engaging in any study-related procedures.

Exclusion criteria comprised unplanned hospitalization one month prior to the baseline visit, discontinuation or initiation of device or pharmacologic treatment for heart failure one month before the baseline visit, and coronary or peripheral revascularization, valvular procedures, any major surgical procedure, acute coronary syndrome (ACS), stroke, or transient ischemic attack within three months before the screening visit. In addition, individuals with any acute illness or diseases that would reduce life expectancy to less than one year other than HFrEF, organ transplant recipients, and those with primary significant valve disease (defined as at least moderate to severe valve disease) were excluded from the study.

2.2 Assessment of Pulse Wave Analysis

PWA was performed on the second study visit using the SphygmoCor® system (AtCor Medical, Sydney, Australia). The participants were placed in a quiet environment in a supine position for 15 minutes, after which brachial blood pressure was recorded to calibrate the system. The SphygmoCor® system employs applanation tonometry, a technique where a sensitive pressure sensor is positioned over the radial artery. The principle involves gently compressing the artery against the underlying radius bone until optimal flattening occurs. This controlled compression equalizes the forces within the arterial wall, enabling precise capture of the pulse wave's shape and timing characteristics. The non-invasive nature of this approach allows for accurate arterial waveform acquisition without disrupting normal blood flow dynamics.

The system captures radial artery pressure waveforms and, using a validated generalized transfer function, mathematically derives the corresponding central aortic pressure waveform. This transformation algorithm accounts for wave reflection phenomena and arterial stiffness variations between the radial and aortic sites. From the derived aortic waveform, several hemodynamic parameters were calculated, including AIx.

The device was used to obtain at least two PWA recordings. A third measurement was conducted if there were major differences between the parameters of the initial two measurements, such as an AIx difference of more than 4%. The results with the measured values closest to each other were used for subsequent analysis.

2.3 Assessment of Pulse Wave Velocity

Immediately following PWA, carotid-femoral PWV measurements were performed using the same SphygmoCor® system. Participants remained in the supine position while the distance from palpable carotid and femoral pulses to the suprasternal notch (fossa jugularis sternalis) was measured using a standard measuring tape.

The SphygmoCor® system sequentially recorded pressure waveforms at both the carotid and femoral arterial sites using the same tonometry sensor.

To determine PWV, the system employs the "Intersecting Tangents" algorithm, a widely accepted analytical method for waveform analysis. This algorithm precisely identifies the foot of each pressure waveform by drawing two tangent lines: one along the initial upstroke of the pressure wave and another along the horizontal baseline during diastole. The point where these tangents intersect defines the onset of the pressure wave at each arterial site. The time delay between these two onset points represents the pulse transit time. The PWV, expressed in meters per second (m/s), is then calculated as the ratio of the measured arterial path length to this transit time.

Each measurement was performed twice. If the difference between two recordings exceeded 1.5 m/s, a third measurement was obtained. For subsequent analysis, the two closest values were selected for analysis.

2.4 Transthoracic Echocardiography

Transthoracic echocardiography was performed on each participant during their first visit by experienced cardiologists using a Vivid 7 or Vivid E9 (GE Healthcare, Chalfont St Giles, UK) with an image acquisition rate of at least 70 frames per second. Simultaneous ECG recording was used to accurately define end-diastole and end-systole.

The protocol for transthoracic echocardiography included acquisition of 2D, 3D, and Doppler images according to standardized guidelines. For participants in normal sinus rhythm, a minimum of three consecutive cardiac cycles were recorded, while five consecutive cycles were acquired for patients with atrial fibrillation to account for beat-to-beat variability. Multiple standardized views were systematically obtained, including: parasternal long axis view (PLAX), parasternal short axis views (PSAX) at multiple levels (heart valves, mitral valve, papillary muscles, and apex), apical views (two-chamber, three-chamber, four-chamber, and five-chamber) and subcostal view for comprehensive cardiac assessment. The acquired image loops and still frames were digitally archived in the digital archive IntelliSpace Cardiovascular (ISCV; Philips, Eindhoven, Netherlands).

2.5 Blood Sampling and Assessment of Laboratory Parameters

32mL of blood and 8mL of spot urine were processed directly after collection on the second visit for the purpose of immediate determination of parameters, at the Clinical Institute of Medical and Chemical Laboratory Diagnostics (18mL) and at the Laboratory platform of the Division of Endocrinology (14mL).

This study focused on specific parameters measured using 8 mL of Lithium Heparin plasma at Clinical Chemistry, including NT-proBNP and eGFR.

2.6 Vital signs

The office blood pressure and heart rate were measured according to the current European Society of Hypertension and European Society of Cardiology guidelines.[50] A validated semi-automatic blood pressure monitor was used to measure the blood pressure on both upper arms. The arm with the higher measured value was selected for further measurements. In one-minute intervals the blood pressure was recorded two more times. The first measurement was discarded and the average of the second and third blood pressure measurement was documented in the case report form as office blood pressure. The average of the two heart rates was noted as office heart rate.

2.7 Data Analysis and Statistics

Data was exported and cleaned in Excel (Microsoft Office 365, Microsoft Corporation, Redmond, US) and then imported to IBM SPSS statistics 26 (IBM Corporation, Armonk/New York, US) for further statistical analysis. Results were considered statistically significant with (two-sided) p-values <0.05.

All data was tested for normal distribution and variance homogeneity. For normal distribution, graphic evaluation and the Shapiro-Wilk-test were used. For group-comparison, unpaired t-test was used for normally distributed parameters and Man-Whitney-U-test was used for parameters that did not fulfill the criteria of normal distribution.

The following parameters were deemed to be normally distributed: systolic blood pressure, diastolic blood pressure, eGFR, AIx, and AIx@75.
Age, body mass index (BMI), heart rate, LVEF, NT-proBNP, pulse pressure as well as augmentation pressure did not meet the criteria of normal distribution.
Pearson’s Product-Moment Correlation was used for correlation analysis of normally distributed parameters, and Spearman’s Rank-Order Correlation was utilized for non-normally distributed data.

A survival analysis was conducted using univariable Cox proportional hazards regression to evaluate the impact of AIx and AIx@75 on a composite endpoint of worsening heart failure and all-cause mortality. Subsequently, multivariable Cox regression analyses were conducted to adjust for confounders deemed clinically significant, including age, gender, BMI, systolic blood pressure, LVEF and eGFR.
Furthermore, a univariable Cox regression analysis was performed to assess the association between PWV and the composite endpoint.

3. Results

3.1 Subjects

A total of 169 participants had feasible PWA data and were included in the analysis. The median (interquartile range) age of the cohort was 66.5 (58.1 – 73.2) years. The study cohort consisted of 38 women, which accounted for 22.5% of the study population.

Median BMI was 27.8 (25.0 – 31.6) kg/m². Among the cohort, only one (0.6%) individual was classified as underweight (BMI < 18.5 kg/m²), while 40 (23.7%) participants had a normal BMI (18.5 – 24.9 kg/m²) and 71 (42%) participants presented with a BMI between 25 and 29.9 kg/m². Furthermore, 57 (33.7%) participants were categorized as obese (BMI ≥ 30 kg/m²). There were no major differences in BMI observed between genders. Male participants displayed a median BMI of 27.8 (25 - 31.3) kg/m². In comparison, female participants had a median BMI of 28.1 (23.3 – 33.6) kg/m².

Mean (± standard deviation) systolic blood pressure was 122.7 (±20.5) mmHg and mean diastolic blood pressure was 76.5 (±12.9) mmHg. The median heart rate was 63.5 (58.5 – 74) bpm.

Median LVEF was 35.6 (30.7 – 43.0) %. Male patients exhibited a median LVEF of 35 (29.4 – 41.7) %, while women had a median LVEF of 37.8 (33.3 – 45.5) %.
158 (93.5%) participants had NT-proBNP values above 125 pg/mL, which is defined as elevated by the European Society of Cardiology.[1] The median NT-proBNP level in the cohort was 968 (323 – 2133) pg/mL.

The majority of the cohort had non-ischemic heart failure (%). Among the non-ischemic cases, idiopathic dilated cardiomyopathy was the most prevalent, accounting for 83 (49.1%) cases. Other notable non-ischemic conditions included inflammatory cardiomyopathy (7.7%), hypertrophic cardiomyopathy (1.2%), and cardiac sarcoidosis (0.6%).

The mean eGFR was 65 (±22.6) mL/min/1.73 m². According to the KDIGO classification[51], 30 (18.3%) participants had normal or high eGFR levels (≥90 mL/min/1.73 m²). A total of 66 (40.2%) participants had mildly reduced kidney function, with eGFR values between 60 and 89.9 mL/min/1.73 m². Additionally, 36 (22%) participants were classified as having mildly to moderately reduced kidney function (eGFR 45–59.9 mL/min/1.73 m²), while 21 (12.8%) patients showed moderately to severely reduced kidney function (eGFR 30–44.9 mL/min/1.73 m²). Severe reduction in kidney function (eGFR 15–29.9 mL/min/1.73 m²) was observed in 10 (6.1%) patients, and 1 (0.6%) patient exhibited kidney failure with an eGFR <15 mL/min/1.73 m².

A total of 116 (68.6%) participants had a prior diagnosis of arterial hypertension. A diagnosis of chronic kidney disease was present in 61 (36.1%) participants. Diabetes mellitus was reported in 51 (30.2%) participants. Atrial fibrillation was observed in 67 (39.6%) participants. When analyzed by gender, 54 (41.2%) men exhibited atrial fibrillation, while it occurred in 13 (34.2%) women. Detailed baseline characteristics are summarized in Table 1.

3.2 Pulse Wave Analysis

3.2.1 Central pressures and Augmentation Index

Median pulse pressure was 35.3 (28.0 – 44.0) mmHg and median augmentation pressure was 10.5 (6.4 – 15.4) mmHg. Mean AIx was 29.3 (± 10.2) %. Women showed a significantly higher mean AIx than men (32.5 [± 10.2] % versus 28.3 [± 10] %, p=0.027). Mean AIx@75 was 24.2 (± 9.7) %, with higher mean values in women compared to men (28.6 [± 10] % versus 23 [± 9.2] %, p= 0.001).

Pulse pressure showed a significant positive correlation with LVEF (r= 0.303, p <0.001). Similarly, augmentation pressure was significantly correlated with LVEF (r= 0.264, p = 0.002). These correlations are visualized in Figure 3. No significant correlations were observed between AIx and LVEF (r = 0.140, p = 0.102) or AIx@75 and LVEF (r = 0.114, p = 0.181). Full correlation analysis is provided in the Appendix (Supplementary Table 1).

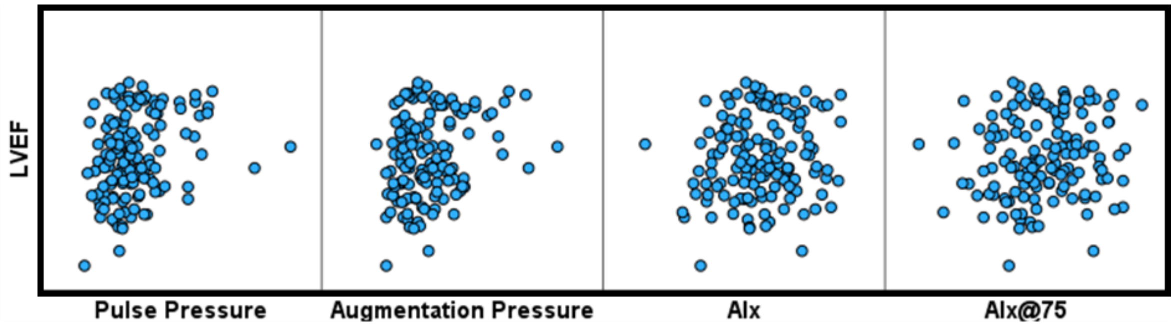

***Figure 3**: Scatter plots presenting the correlation between LVEF and pulse pressure, augmentation pressure, AIx and AIx@75. Abbreviations: AIx - augmentation index, AIx@75 - heart rate-corrected augmentation index, LVEF - left ventricular ejection fraction.*

3.2.2 Pulse Wave Velocity

PWV was feasible in 78 (46.2%) patients, 64 (82.1%) of whom were men. Mean PWV was 7.4 (± 1.9) m/s. Men had a significantly higher PWV compared to women (7.6 [± 1.9] m/s versus 6.6 [± 1.5] m/s, p=0.040).

Patients with diabetes mellitus (n=22) had significantly higher PWV compared to patients without diabetes mellitus (n=55) (8.3 [±2.0] m/s versus 7.0 [±1.8] m/s, p = 0.005). This difference is illustrated in Figure 4. In patients with arterial hypertension (n=52), PWV was also elevated, recording a mean value of 7.7 (± 2.0) m/s versus 6.9 (±1.8) m/s in those without arterial hypertension (n=21). However, this difference did not reach statistical significance (p = 0.111).

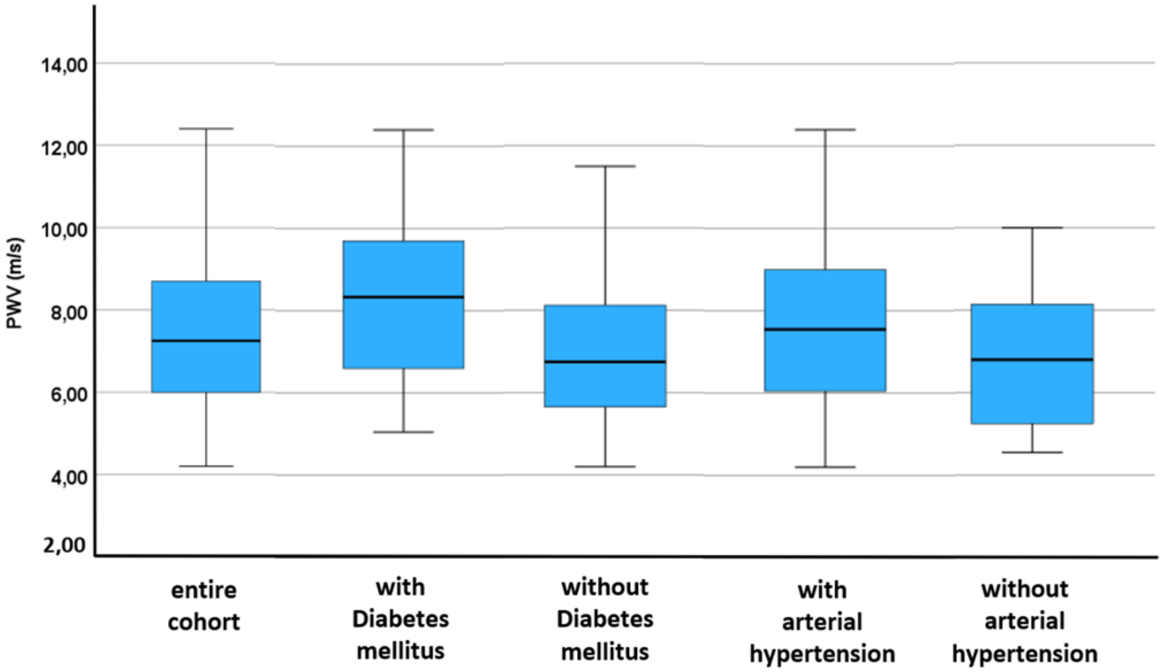

Figure 4: *Boxplots showing PWV in the whole population and comparing PWV in patients with and without diabetes mellitus and in those with and without arterial hypertension. Abbreviations: PWV - pulse wave velocity.*

	Total Cohort (n=169)	*Missing Data, n(%)*	*Patients Eligible for PWV (n=78)*	*Missing Data for PWV, n(%)*
Age, years	66.5 (58.1-73.2)	0 (0)	66.8 (58.3-74.4)	0 (0)
Women, n(%)	38 (22.5)	0 (0)	14 (17.9)	0 (0)
Ischemic Origin of HF, n(%)	70 (41.4)	0 (0)	33 (42.3)	0 (0)
Idiopathic DCM	83 (49.1)	0 (0)	34 (43.6)	0 (0)
Inflammatory CMP	13 (7.7)	0 (0)	9 (11.5)	0 (0)
Hypertrophic CMP	2 (2.1)	0 (0)	1 (1.3)	0 (0)
Cardiac Sarcoidosis	1 (0.6)	0 (0)	1 (1.3)	0 (0)
BMI, kg/m2	27.8 (25.-31.6)	0 (0)	26.1 (23.7-28.4)	0 (0)
Systolic Blood pressure, mmHg	122.7 ±20.5	3 (1.8)	123.8 ±21.5	1 (1.3)
Diastolic Blood pressure, mmHg	76.5 ±12.9	3 (1.8)	77 ±11.4	1 (1.3)
Heart rate, bpm	63.5 (58.5-74)	4 (2.4)	62 (55.8-71.9)	2 (2.6)
LVEF, %	35.6 (30.7-43)	31 (18.3)	38.1 (31.6-44.4)	16 (20.5)
NT-proBNP, pg/mL	968 (322.5-2132.5)	0 (0)	778 (300.8-1646.8)	0 (0)
eGFR, ML/min/1.73m2	65 ±22.6	5 (3)	67.8 ±21.9	0 (0)
Arterial Hypertension, n(%)	116 (68.6)	8 (4.7)	52 (76.7)	5 (6.4)
Diabetes mellitus, n(%)	51 (30.2)	1 (0.6)	22 (28.2)	1 (1.3)
Hyperlipidemia, n(%)	83 (49.1)	20 (11.8)	33 (42.3)	8 (10.3)
Chronic kidney disease, n(%)	61 (36.1)	2 (1.2)	26 (33.3)	1 (1.3)
Atrial fibrillation, n(%)	67 (39.6)	0 (0)	26 (33.3)	0 (0)
Pulse pressure, mmHg	35.3 (28.2-44.3)	0 (0)	37.5 (31.3-47.1)	0 (0)
Augmentation pressure, mmHg	10.5 (6.4-15.4)	0 (0)	11.3 (7-17.1)	0 (0)
AIx, %	29.3 ±10.2	0 (0)	29.7 ±10.9	0 (0)
AIx@75, %	24.2 ±9.7	0 (0)	24.1 ±10.5	0 (0)
PWV, m/s	-	-	7.4 ±1.9	0 (0)

Table 1: *Baseline characteristics of the total cohort (n=169) and the subgroup eligible for PWV analysis (n=78). Continuous variables are presented as median*

(interquartile range) or mean ± standard deviation, as appropriate. Percentages refer to the respective subgroup. Abbreviations: HF - heart failure, DCM - dilatated cardiomyopathy, CMP - cardiomyopathy, BMI - body mass index, LVEF - left ventricular ejection fraction, NT-proBNP - N-terminal pro-B-type natriuretic peptide, eGFR - estimated glomerular filtration rate, AIx - augmentation index, AIx@75 - heart rate-corrected augmentation index, PWV - pulse wave velocity.

3.3 Outcome Analysis

Over a median observation period of 5.0 (4.0 – 5.3) years, worsening heart failure occurred in 37 (21.9%) cases and 46 (27.2%) participants died. Sixty-three (37.3%) participants reached the composite endpoint of worsening heart failure and all-cause death. A detailed overview is provided in Table 2.

	Total Cohort (n=169)	*Patients Eligible for PWV (n=78)*
Observation time, years	5 (4-5.3)	4.4 (3.9-5.1)
Worsening heart failure, n(%)	37 (21.9)	17 (21.8)
Death, n(%)	46 (27.2)	16 (20.5)
Composite Endpoint, n(%)	63 (37.3)	26 (33.3)

Table 2: *Clinical outcomes in the total cohort (n = 169) and in the subgroup eligible for PWV analysis (n = 78). Data are presented as median (interquartile range) for observation time and as absolute numbers with corresponding percentages for event rates. Abbreviations: PWV - pulse wave velocity.*

3.3.1 Augmentation Index

In univariate Cox regression analysis both, higher AIx and AIx@75, were significant predictors of the composite endpoint (AIx: HR 0.971; AIx@75 HR 0.974). The association between AIx and clinical outcomes is illustrated in Figure 5. In the multivariable Cox regression model adjusted for age, gender, BMI, systolic blood pressure, LVEF, and eGFR, both remained significant predictors (AIx: HR 0.958 (95% CI: 0.924 – 0.994, p=0.023; AIx@75: HR 0.962 (95% CI: 0.926 – 1.000, p=0.048). Detailed outcome analysis is provided in the Appendix (Supplementary Table 2 and 3).

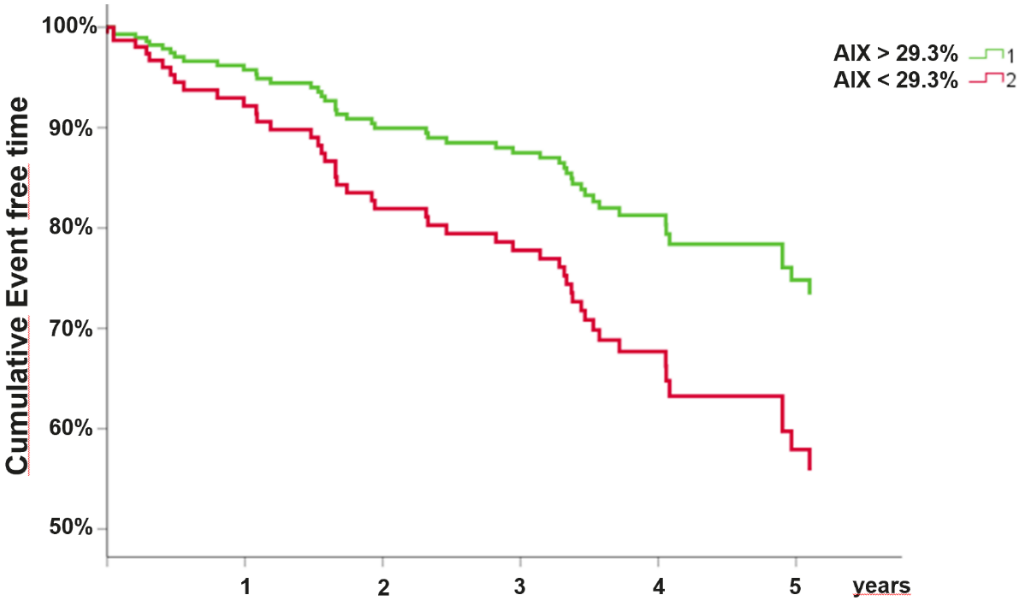

Figure 5: *Cumulative event-free survival over five years stratified by mean AIx. The plot illustrates the association between AIx and clinical outcomes, based on Cox proportional hazards analysis. Abbreviations: AIx - augmentation index.*

3.3.2 Pulse Wave Velocity

Among the 78 patients with available PWV data, 26 (33.3%) reached the composite endpoint. In univariable Cox regression analysis, PWV did not reach statistical significance (HR 0.955 (95% CI 0.779 – 1.172, p=0.662).
Detailed outcome analysis is provided in the Appendix (Supplementary Table 4).

4. Discussion

This study investigated the association between PWA parameters, specifically AIx and PWV, and a composite endpoint of worsening heart failure or all-cause death in patients with CHF. Results highlighted notable gender differences, with AIx and AIx@75 values being generally higher in women than in men. Additionally, both pulse pressure and augmentation pressure showed a positive correlation with LVEF, suggesting a relationship between pulse wave parameters and cardiac function. While PWV levels were relatively low on average in this population, they were elevated in patients with diabetes mellitus and hypertension. Importantly, outcome analysis indicated that lower AIx values were associated with worse clinical outcomes in both univariable and multivariable Cox regression models, whereas PWV was not predictive of prognosis. These findings contribute to a nuanced understanding of PWA parameters in risk assessment and may support the role of AIx as a prognostic tool in heart failure.

4.1 The Effects of Age and Gender on AIx

The mean AIx of 29.3% observed in our cohort aligns with expected values for a population with a median age of 66.5 years, as AIx is known to rise with age due to arterial changes. This age-related increase was also demonstrated in a large study from the Copenhagen City Heart Study[52], which included 3,432 participants. Using the SphygmoCor device for noninvasive PWA, the study explored the association between AIx and cardiovascular risk factors. The study found a substantial increase in AIx with age: in men under 60, the median AIx was 17%, compared to 26% in men aged 60 and older. Similarly, in women under 60, the median AIx was 26%, rising to 36% in those above 60.

This pattern supports the notion that, with age, the initial pressure wave contributes more to the increased pulse pressure, rather than there being a weakening in pulse wave reflections. This shift is attributed to central arteries becoming stiffer and less compliant with age, leading to an increase in this initial pressure wave.[53] We were able to confirm this hemodynamic pattern in patients with HFrEF.

Another notable finding from the Copenhagen City Heart Study was the gender disparity, with both younger and older women showing significantly higher AIx values than their male counterparts.[52]

Further support for this pattern comes from the Anglo-Cardiff Collaborative Trial (ACCT)[54], which studied 4,001 healthy, normotensive individuals aged 18 to 90 years and consistently found higher AIx values in women across all ages. One explanation proposed by the ACCT is that women's shorter average height results in a shorter distance between the heart and wave reflection sites, which may amplify wave reflection. Even after adjusting AIx for height, however, values remained significantly higher in women, indicating that gender itself is an independent predictor of AIx. Importantly, the ACCT found no significant differences in PWV between men and women, suggesting that the elevated AIx in women is likely due to differences in wave reflection mechanics rather than a direct effect on arterial stiffness.

Our findings support this observation, with notable differences between sexes also in HFrEF. In our cohort, women had a mean AIx of 32.4%, which was significantly higher than the 28.3% observed in men ($p=0.027$). In line with this, the mean PWV in our cohort was actually higher in men (7.6 m/s) compared to women (6.6 m/s), further supporting the theory that heightened AIx in women is influenced more by wave reflection dynamics than by increased arterial stiffness.

4.2 Relationship Between PWA Parameters and Cardiac Function

In our analysis, we observed a significant positive correlation between LVEF and both pulse pressure ($r = 0.303$, $p \leq 0.001$) and augmentation pressure ($r = 0.264$, $p = 0.002$). This may indicate that a decline in left ventricular function results in a reduction of arterial pressure generated by the heart. These results suggest that in patients with reduced LVEF, pulse pressures and wave reflections represent not only arterial stiffness but also the systolic function of the left ventricle. However, AIx and AIx@75 were not significantly correlated with LVEF in this cohort.

Parragh and colleagues[45] examined 183 subjects, including 61 patients with reduced LVEF and 122 matched controls with normal LVEF. Consistent with our findings, they showed that in patients with reduced LVEF a strong positive correlation between LVEF and pulse pressure, measured invasively and noninvasively was present (both $p<0.005$). Furthermore, augmentation pressure and AIx showed positive correlations with LVEF ($p<0.001$ and $p=0.005$, respectively). In contrast, the control group with normal LVEF exhibited little to no relationship, or even an inverse relationship, between measures of left ventricular function and PWA parameters. Notably, there were no significant differences in arterial impedance, aortic stiffness, or wave reflections between patients with preserved and reduced LVEF. Therefore, the authors suggest that in patients with preserved LVEF, PWA parameters can effectively reflect arterial function, wave reflections, and arterial stiffness. On the other hand, patients with reduced LVEF consistently exhibited lower pulse pressure, augmentation pressure, and AIx values. This points to a link between reduced left ventricular function and diminished arterial pulsatility, as also observed in our cohort.

4.3 Comorbidities and Pulse Wave Velocity

The Framingham Heart Study measured PWV noninvasively in 2232 healthy participants, with a median carotid-femoral PWV of 9.3 m/s.[55] In comparison, our HFrEF cohort exhibited notably lower PWV values with a mean of 7.4 m/s. Possible explanations for this could be that HFrEF patients experience lower blood pressure over time due to reduced cardiac output and heart failure therapy. Arterial hypertension showed to be a major contributor to higher PWV in the general population.[56] In CHF, a reduction in muscular artery stiffness may occur due to decreased smooth muscle tone and increased dilatation, especially in peripheral arteries.

This claim is supported by a study proving PWV lower in CHF patients compared to a healthy control group. They mostly attributed this to reduced stiffness in muscular vessels and not central ones, as there was no difference in total arterial compliance.[57]

As mentioned before, the connection between arterial hypertension and PWV is well-recognized, as higher blood pressure is a major factor contributing to increased arterial stiffness. The European Society of Cardiology recommends that PWV assessment be included in the evaluation of specific hypertensive patients in hospital care.[56]

In our cohort, this relationship holds true, as patients with arterial hypertension had a mean PWV of 7.7 m/s, compared to 6.9 m/s in those without hypertension. The difference likely did not reach statistical significance due to the limited sample size of patients with available PWV data in our cohort. In a larger HFrEF cohort of 306 patients, a significant difference was demonstrated ($p < 0.01$). There was a mean PWV of 12.4 (± 3.2) m/s in 114 patients with arterial hypertension, defined as systolic blood pressure ≥140 mmHg, compared to 11.4 (± 3.0) m/s in the 192 patients without arterial hypertension.[28]

Another comorbidity known to significantly increase PWV is diabetes mellitus. In a Chinese study, 79 diabetes mellitus patients were matched with 79 control participants.[58] All methods of PWV measurement (carotid-femoral, carotid-radial, and carotid-ankle) showed significant differences between the two groups. The mean carotid-femoral PWV was 11.78 m/s in DM patients, compared to 9.95 m/s in the control group ($p < 0.001$). Our findings confirm that this relationship persists in HFrEF, showing a substantial difference in PWV between patients with diabetes mellitus (8.3 m/s) and those without (6.98 m/s).

Notably, some studies on CHF have reported higher PWV values, particularly in HFpEF and, to a lesser extent, in HFrEF patients.[45,59]
There is no unifying explanation yet for these differences, and further prospective studies investigating how decreasing cardiac performance affects PWV are needed.

Key factors to consider when comparing these findings include the method of PWV measurement and the comorbidities present in the cohorts.

4.4 Prognostic Value of AIx in Chronic Heart Failure

In our cohort, low values of AIx and AIx@75 were each found to be significant predictors of the composite endpoint of worsening heart failure and death. Even after adjusting for confounders such as age, gender, BMI, systolic blood pressure, LVEF, and eGFR, both PWA parameters remained significant predictors. Our present analysis implies that lower values of AIx and AIx@75 are indicative of a worse prognosis in HFrEF patients, hinting at hemodynamic changes specific to HFrEF.

Parragh and colleagues[45] offer a plausible explanation for the AIx patterns observed in patients with reduced LVEF. They describe that when the left ventricle cannot overcome the late systolic load, it fails to raise arterial pressure sufficiently, resulting in an early end to blood ejection. This restriction reduces pulse pressure amplification, as indicated by a shorter ejection duration and lower stroke volume. The reduction in pulse pressure amplification ultimately results in a lower AIx. To maintain cardiac output despite the reduced stroke volume, heart rate increases. A rise in heart rate is known to reduce the time for wave reflections, decreasing augmentation pressure and further lower AIx.
However, in our cohort, lower AIX@75 values were also predictive of worse outcome, suggesting that reduced ejection time and diminished pulse pressure amplification are the primary hemodynamic mechanisms underlying these findings.

This indicates that in HFrEF patients higher AIx values can be indicative of better cardiac performance. An increase in left ventricular function leads to a prolongation of ejection and an increase pulse pressure amplification which ultimately is depicted as an increase in AIx, as explained by Parragh and colleagues. However they did not conduct an outcome analysis.[45]

Our study was able to provide further insight into the association of higher AIx values with fewer cases of worsening heart failure and death. The persistence of this association, even in adjusted models, highlights AIx and AIx@75 as relevant surrogate markers in HFrEF, offering prognostic insight that extend beyond traditional measures of arterial stiffness.

Remarkably, in HFpEF cohorts a different pattern has been observed. A prospective study involving 336 patients with HFpEF, with a mean age of 63.5 years, found that peak systolic velocity, an indicator of left ventricular contractility, exhibited an inverse relationship with AIx, augmentation pressure and PWV. In this context, the inverse relationship means that better contractility is associated with lower wave reflections and reduced arterial stiffness. Similarly, early diastolic velocity showed a strong negative correlation with augmentation pressure and PWV. This negative correlation indicates that increased filling pressures, which can arise from fluid overload or heart failure exacerbation, were associated with greater AIx, greater augmentation pressure and higher PWV. All associations remain significant regardless of age and gender. Additionally, concerning clinical symptoms, patients suffering from exertional dyspnea showed elevated AIx, augmentation pressure, and PWV.[43]

It appears that in HFpEF, PWA parameters maintain their traditional role as markers of arterial stiffness, with higher AIx associated with worse cardiac performance.
Regarding outcomes, a large retrospective cohort study of 24 480 HFpEF patients found that as pulse pressure increased, the hazard ratio for all-cause mortality after one year also heightened.[60]

4.5 Prognostic Value of PWV in Chronic Heart Failure

The prognostic value of PWV in CHF was highlighted in the EPHESUS trial.[28] This study analyzed PWV in 306 participants with a mean age of 61 (±11) years, a mean LVEF of 34.4 (±5.2) %, and an arterial hypertension rate of 60% among its participants. They found a significant association between higher PWV and increased all-cause mortality (HR 1.16 [95% CI: 1.03-1.30, $p<0.05$]). After further analysis, the majority of deaths were identified as cardiovascular deaths. This relationship remained significant, independent of age and ejection fraction.

In contrast, our analysis was not able to confirm the predictive value of PWV in HFrEF patients. Given that our cohort had similar baseline characteristics to those in the EPHESUS trial, including comparable LVEF, age, and arterial hypertension rates, it is probable that the lack of statistical significance in our findings was due to the rather small sample size. This may have reduced our ability to detect subtle associations, suggesting that a larger study would be needed to validate or challenge the results reliably.

4.6 Strengths, Limitations and Clinical Implications

Our study has several notable strengths. First, the cohort represents a typical real world HFrEF population with common comorbidities. This enhances the applicability of our findings to routine care settings. Additionally, with a median observation time of five years, our study offers a robust timeframe for observing outcomes, contributing valuable prognostic insights.

Our cohort included 22.5% women, reflecting the common underrepresentation of women in cardiovascular trials. This may limit the applicability of our findings to female patients.
Nonetheless, we were able to identify significant sex-related differences in AIx and AIx@75, highlighting the relevance of sex-based distinctions in vascular characteristics among HFrEF patients.

The primary limitation of our study is the small sample size for which PWV data were available, which may have limited our statistical power to detect associations, particularly prognostic effects of PWV. While we demonstrated that lower AIx values are associated with worse outcomes, we were unable to establish precise cutoff values to define when "low" becomes prognostically concerning. This limits the immediate clinical applicability of our findings in guiding individual patient risk stratification. Further studies with larger cohorts would be necessary to refine these insights and explore definitive threshold values for AIx in the HFrEF population.

4.7 Conclusion

In patients with CHF and reduced ejection fraction, lower AIx values were independently associated with worse outcomes, suggesting its value as a prognostic marker. AIx may reflect key hemodynamic changes in HFrEF patients beyond arterial stiffness. In contrast, PWV showed no significant association with prognosis in our cohort, despite being elevated in patients with hypertension and diabetes. Further studies are needed to validate the prognostic utility of PWA parameters and clarify their role in clinical risk stratification.

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Appendix

		biplane LVEF	Pulse pressure	Augmentation Pressure	AIx	AIx@75
biplane LVEF	Coefficient	-	,288**	,264**	,140	,114
	Sig.	-	<,001	,002	,102	,181
	N	-	138	138	138	138
Pulse pressure	Coefficient	,288**	-	,885**	,400**	,220**
	Sig.	<,001	-	<,001	<,001	,004
	N	138	-	169	169	169
Augmentation pressure	Coefficient	,264**	,885**	-	,749**	,559**
	Sig.	,002	<,001	-	<,001	<,001
	N	138	169	-	169	169
AIx	Coefficient	,140	,400**	,749**	-	,846**
	Sig.	,102	<,001	<,001	-	<,001
	N	138	169	169	-	169
AIx@75	Coefficient	,114	,220**	,559**	,846**	-
	Sig.	,181	,004	<,001	<,001	-
	N	138	169	169	169	-

Appendix Table 1: *Correlations between different PWA measurements and LVEF. Pearson correlation. Abbreviations: LVEF - left ventricular ejection fraction, AIx - augmentation index, AIx@75 - heart rate-corrected augmentation index.*
*** correlation significant (two-sided) on the level of 0.01*

	HR (95% CI)	p-value
AIx (%)	0.971 (0.947–0.996)	0.023
AIx@75 (%)	0.974 (0.949–1.000)	0.049

Appendix Table 2: *Univariate cox regression analysis of AIx and AIx@75 regarding the composite endpoint of worsening heart failure and over-all mortality.*
Model fit: –2 Log Likelihood = 602.4 (AIx), 603.8 (AIx@75);
χ^2 = 5.2 and 3.9 respectively, $p < 0.05$. Abbreviations: AIx - augmentation index, AIx@75 - heart rate-corrected augmentation index, HR - hazard ratio.

	HR (95% CI)	p-value
AIx (%)	0.958 (0.924–0.994)	0.023
AIx@75 (%)	0.962 (0.926–1.000)	0.048
Age (years)	1.027 (0.992–1.064)	0.127
BMI (kg/m²)	1.039 (0.977–1.105)	0.221
Male sex	0.611 (0.257–1.453)	0.265
Systolic blood pressure	0.999 (0.985–1.014)	0.889
LVEF (%)	0.962 (0.928–0.997)	0.035
eGFR (CKD-EPI)	0.971 (0.956–0.986)	<0.001

Appendix Table 3: *Multivariate cox regression analysis of AIx and AIx@75 regarding the composite endpoint including including the confounders Age, BMI, Gender, Systolic blood pressure, LVEF and eGFR.*
Model fit: –2 Log Likelihood = 393.0; $\chi^2 = 39.2$, df = 7, $p < 0.001$. Abbreviations: AIx - augmentation index, AIx@75 - heart rate-corrected augmentation index, BMI - body mass index, LVEF - left ventricular ejection fraction, eGFR - estimated glomerular filtration rate, HR - hazard ratio.

	HR (95% CI)	p-value
PWV (m/s)	0.955 (0.779–1.172)	0.662

Appendix Table 4: *Univariate Cox regression analysis of PWV regarding the composite endpoint.*
Model fit: –2 Log Likelihood = 208.2; $\chi^2 = 0.2$, $p = 0.662$. Abbreviations: PWV - pulse wave velocity, HR - hazard ratio.

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