Diplomarbeit

Detection of heart failure during the ECG recording using the Combyn™ ECG

eingereicht von

Samy Mady

zur Erlangung des akademischen Grades

Doktor der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Innere Medizin

Klinische Abteilung für Kardiologie

und dem Institut für Herzkreislauf- und Stoffwechselmedizin

unter der Anleitung von

Univ. Prof. Dr. Falko Skrabal

und

Univ. Prof. Dr. med. univ. Friedrich Fruhwald

Graz, am 07.09.2022

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 07.09.2022 *Samy Mady eh.*

Foreword

I met Prof. Skrabal for the first time at the beginning of the 5th semester during his elective course “Selected chapters of internal medicine with special focus on cardiovascular and metabolic diseases” 3 years ago.
In this weekly lecture, he presented and discussed common as well as diagnostically challenging cases that he had seen over the many years he had worked in internal medicine.
Due to my early stage in medicine and sometimes complex topics I didn´t understand everything he said at the beginning, but after consistent attendance and research after each lecture my interest for internal medicine soon sparked.

After some months Prof. Skrabal asked if someone would like to assist him at his institute and I immediately volunteered. In the following months, I had the privilege to examine patients together with him, perform ECGs, echocardiography, discuss diagnoses and treatments and observe his interaction with patients.
It didn’t take me long to realize that he was different from all doctors I have heard about or seen before until today. The way he cared for patients, his unique compassion, enthusiasm and curiosity for medicine quickly infected me.
Prof. Skrabal soon noticed my commitment and enthusiasm and asked me to accompany him at an international cardiology conference in Belgrade. It was an amazing and inspirational experience listening and talking to the leading researchers in the field of cardiovascular medicine from all around the world.
Because of his extensive medical and scientific knowledge, I asked him if I could write my thesis under his supervision at his Institute of Cardiovascular and Metabolic Medicine.
In the following years, he taught me a lot about medicine, how to become a good doctor, but most importantly how to become a better person.
His passion for teaching, research and medicine remains unique and he certainly became a mentor and role model for me. I will always aspire to become the compassionate teacher he is and someday reach his level of kindness, attitude towards learning and medical expertise.

Acknowledgement

First, I would like to thank my mentor Univ. Prof. Dr. Skrabal Falko for his supervision and constant support during the process of writing my thesis. Numerous meetings were necessary to answer the many questions that emerged during its writing and without his assistance and experience in scientific research I would not have managed to complete this paper.

Additionally, I want to thank Dr. Katharina Skrabal for always helping me with handling the huge amount of data, technical assistance and much more.

Furthermore, I want to thank Univ. Prof. Dr. med. univ. Fruhwald Friedrich, from the department of cardiology at the state hospital Graz, for his agreement to be my co-supervisor and to allow the measurements at the outpatient clinic.

Special thanks go also to my dear friend Jurij Maurer and Moritz Seel, who assisted me in data acquisition in the above-mentioned clinic.

Lastly I want to thank my amazing girlfriend Sara, who always supported me in every possible way and my mother Isolde, my father Omer, my brother Dany, my grandmother Johanna and my grandfather Friedrich, without whom the completion of this thesis would not have been possible.

Table of Contents

Abbreviations

ACEI	angiotensinogen converting enzyme inhibitor
ADH	antidiuretic hormone
AI	artificial intelligence
ANOVA	analysis of variance
ANP	atrial natriuretic peptide
ARB	angiotensin II receptor blocker
AUC	area under the curve
AVC	arrhythmogenic ventricular cardiomyopathy
BNP	brain natriuretic peptide
CHF	chronic heart failure
CAD	coronary artery disease
CADS	computer-aided detection systems
CKD	chronic kidney disease
CNN	convolutional neural network
DNN	deep neural network
COPD	chronic obstructive pulmonary disease
DCM	dilated cardiomyopathy
EABV	effective arterial blood volume
ECG	electrocardiography
EDV	end diastolic volume
ESV	end systolic volume
HCM	hypertrophic cardiomyopathy
HOCM	hypertrophic obstructive cardiomyopathy
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
HRV	heart rate variability
LAE	left atrial enlargement
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVNC	left ventricular noncompaction cardiomyopathy
MRA	mineralocorticoid receptor antagonist
MRI	magnetic resonance imaging
PCI	percutaneous coronary intervention
RAAS	renin-angiotensin-aldosteron system
RCM	restrictive cardiomyopathy
ROC	receiver operating characteristics
RV	right ventricle

SVR	systemic vascular resistance
6MVD	6-minute walk distance
2MST	two-minute step test

Table directory

Figure directory

Abstract

Objective: The objective of this thesis was to investigate the potential of detecting HF during routine-ECG using impedance plethysmography and impedance spectroscopy integrated into a 12-lead ECG by comparing the results with gold-standards e.g. serum NT-proBNP levels and the NYHA functional classification.
Background: Despite our best efforts HF still represents a major cause of morbidity and mortality all around the globe. Its timely diagnosis and accurate grading is crucial for providing adequate medical therapy, improving quality of life and preventing chronification of disease.
Material and methods: We obtained measurements of 827 individuals with the Combyn™ ECG at the institute of cardiovascular medicine, Mariatrosterstraße 67 and the outpatient department of cardiology at the state hospital Graz. An electrocardiogram (ECG) was obtained and segmental impedance measurements were performed at 5, 40 and 400 kHz. Additionally, the patients were asked to grade their degree of functional impairment by using the NYHA classification and blood samples were drawn to measure serum NT-proBNP levels. All data were exported to Microsoft Excel and statistical analysis was performed using the statistical software program SPSS.
Results: Comparison of serum NT-proBNP levels with Heart function (estimated degree of HF determined by the Combyn™ ECG) showed a significant association between all the results ($p<0.001$) with AUCs of 0.85, 0.63, 0.56 and 0.86 for NT-proBNP classes 1-4, respectively. Additionally, comparison of Heart function by Combyn™ ECG with the NYHA classification also showed significant associations with a p-value<0.001 and AUCs of 0.74, 0.4, 0.77 and 0.88 for NYHA classes I-IV. Comparison of NT-proBNP classes and NYHA classification revealed significant association (p-value<0.001), except when comparing group III with group IV, with AUCs of 0.81, 0.65, 0.82 and 0.94 for NYHA classes I-IV. Mean NT-proBNP levels in NYHA group I were 286±470.4 pg/mL (n=400), in group II 1036.7±3096.1 (n=222), in group III 2190.1±5424.3 pg/mL (n=109) and in group IV 5318.5±4765.8 pg/mL.
Heart function by Combyn™ ECG also showed significant association with the ECF/ICF ratio in lower extremities (p-value<0.001) with AUCs of 0.87, 0.6, 0.67 and 0.89 for Heart function classes 1-4. Comparison of blood acceleration over the

thorax and over the left leg with Heart function mostly showed signification associations (p-values<0.001). AUCs were 0.64, 0.68, 0.82 and 0.82 for Heart function classes 1-4 when compared with blood acceleration over the thorax and 0.64, 0.55, 0.64 and 0.74 when compared with blood acceleration over the left leg, respectively.

Conclusion: The Combyn™ ECG represents an accurate and novel diagnostic tool for the detection and classification of HF during a routine 12-channel ECG. Especially in individuals with low or very high NT-proBNP levels the device performs well appropriately estimating the degree of HF.

Additionally, it enables cardiovascular phenotyping by measurement of amplitudes of blood accelerations over the thorax and legs, in conjunction to beat-to-beat segmental volume changes in the extremities, which have been shown to correlate with the severity of HF. We observed a broad range of NT-proBNP values among all NYHA functional classes and therefore conclude with a high degree of certainty that most HF patients underestimate their functional impairment.

Zusammenfassung

Zielsetzung: Das Ziel dieser Diplomarbeit war es die Sensitivität und Spezifität des Combyn™ ECGs für die Detektion der Herzinsuffizienz zu untersuchen, indem wir es mit Goldstandardmethoden, wie NT-proBNP-Serumspiegeln und der NYHA-Klassifikation verglichen.

Hintergrund: Trotz zahlreicher globaler Bemühungen stellt die Herzinsuffizienz nach wie vor einen der Hauptgründe für ausgeprägte Morbidität, Mortalität und Gesundheitssystemkosten dar. Eine rechtzeitige Diagnose und genaue Evaluierung des Schweregrades sind für adäquates Therapiemanagement, Lebensqualitätsverbesserung und Chronifizierungsprävention essentiell.

Material und Methodik: Bei insgesamt 827 Personen wurden mit dem Combyn™ ECG Messungen im Institut für kardiovaskuläre Medizin, Mariatrosterstraße 67, und der Kardiologischen Ambulanz des LKH Graz durchgeführt. Dabei wurde ein konventionelles 12-Kanal-EKG geschrieben und zusätzlich segmentale Impedanzmessungen mit 5, 40 und 400 kHz durchgeführt. Die Patient*innen wurden gebeten den Schweregrad ihrer kardialen Funktioneinschränkung einzuschätzen und mittels NYHA-Klassifikation quantifiziert. Zusätzlich wurde Blut abgenommen, um Serum-NT-proBNP-Spiegel zu ermitteln. Die gesamten Daten wurden in Microsoft Excel transferiert und mittels dem Statistikprogramm SPSS analysiert.

Ergebnisse: Der Vergleich der Serum-NT-proBNP-Werten mit der vom Combyn™ ECG berechneten "Heart function" zeigte sich eine signifikante Assoziation der Resultate (p-Wert<0,001) mit AUCs von 0,85, 0,63, 0,56 und 0,86 für die NT-proBNP-Klassen 1 bis 4. Der Vergleich "Heart function" mit NYHA Klassifikation offenbarte ebenfalls eine signifikante Assoziation mit einem p-Wert<0,001 und AUCs von 0,74, 0,4, 0,77 und 0,88 für die NYHA Klassen I bis IV.

Der Vergleich NT-proBNP-Klassen mit NYHA Klassifikation zeigte eine signifikante Assoziation (p-Wert<0,001), außer für den Vergleich Gruppe III mit IV, mit AUCs von 0,81, 0,65, 0,82 und 0,92 für die NYHA Klassen I bis IV

Die mittleren NT-proBNP-Spiegel in der NYHA I Klasse lagen bei 286±470.4 pg/mL (n=400), in der NYHA II Klasse bei 1036.7±3096.1 (n=222), in der NYHA III Klasse bei 2190.1±5424.3 pg/mL (n=109) und in der NYHA IV Klasse bei 5318.5±4765.8 pg/mL.

Der Vergleich „Heart function“ mit ECF/ICF-Ratio in den unteren Extremitäten zeigte eine signifikante Assoziation (p-Wert<0,001) mit AUCs von 0.87, 0.6, 0,67 und 0,89 für die „Heart function“ Gruppen 1 bis 4.
Der Vergleich „Heart function” mit Beschleunigung des Blutes im Thorax und dem linken Bein offenbarte ebenfalls größtenteils signifikante Assoziationen (p-Werte<0,001). AUCs betrugen 0,64, 0,68, 0,82 und 0,82 für die “Heart function” Gruppen 1 bis 4, wenn verglichen mit der Blutbeschleunigung im Thorax und 0,64, 0,55, 0,64 und 0,74 wenn verglichen mit der Blutbeschleunigung im linken Bein.
Schlussfolgerung: Das Combyn™ ECG stellt ein modernes und akkurates diagnostisches Hilfsmittel für die Detektion und Quantifizierung einer Herzinsuffizienz dar. Vor allem in Individuen mit sehr niedrigen bzw. sehr hohen NT-proBNP-Spiegeln zeichnet es sich durch eine beachtenswerte Sensitivität und Spezifität aus. Durch die Messung der Blutbeschleunigung und der Fähigkeit Herzschlag-abhängige Veränderungen des Volumenzustandes in einzelnen Körpersegmenten zu detektieren ermöglicht das Combyn™ ECG eine ausführliche Analyse des kardiovaskulären Status.
Wir beobachteten eine breite Spannweite an NT-proBNP-Werten in allen NYHA Klassen und schlussfolgern, dass viele Patient*innen mit Herzinsuffizienz ihre kardial bedingte funktionelle Einschränkung sehr unterschätzen.

Schlüsselwörter: Herzinsuffizienz, Combyn™ ECG, Elektrokardiographie, Impedanzspektroskopie, Impedanzplethysmographie, NYHA-Klassifikation, NT-proBNP

1 Introduction

1.1. Heart failure: An emerging public health problem

In the last four decades, chronic heart failure (CHF) has become an increasing cause of morbidity and mortality, especially amongst the older population in industrialized nations. The rising numbers of hospitalizations due to an acute heart failure or an exacerbation of a preexisting chronic heart disease contribute a substantial economic burden to health care systems all around the globe.[1]

In the US the total medical costs for patients with chronic heart failure are expected to more than double by the end of this decade (from nearly US$21 billion in 2012 to US$53 billion by 2030).[1]

Although cardiac dysfunction can have a whole variety of reasons, most cases of heart failure have an insidious onset and are attributed to widespread diseases like hypertension, diabetes mellitus and coronary heart disease.[1,2]

Improvement in the medical management of these predisposing conditions and rising understanding of the importance of risk factor modification (e.g. aiming for a normal BMI, smoking cessation, etc.) makes heart failure nowadays a preventable and treatable disease.[1]

Despite an improvement in the mortality for hospitalized patients with heart failure in the US between the years 1999 and 2011 (in-hospital mortality decreased by 38%, 1 month mortality by 16% and 1-year mortality by 13%), the prognosis after the initial diagnosis is still very poor with a high mortality rate of approximately 60%.[1,3]

For this reason, it is very important to detect patients with heart failure early in their disease course. Standard diagnostic tests include ECG, echocardiography, chest x-ray, MRI, coronary angiography and nuclear imaging. Of those some are not widely available, time consuming or expensive.[4]

Currently the most time/cost-efficient diagnostic tool for assessing cardiac function and detecting heart failure certainly is echocardiography.[4]

The important information gained out of this widely available diagnostic test however relies heavily on the operator's experience and knowledge about early signs of structural and functional abnormalities seen on echocardiography.[4]

For this reason, developing a more objective diagnostic tool for detecting heart failure would facilitate and improve the diagnostic process of this deadly disease.[4] Even more widely available, less expensive and easier to asses than echocardiography is electrocardiography (ECG).[4] Electrodes attached to the skin of the patient measure the differential potential between cardiac myocytes generating signals representing the electrical activity of the heart.[4]
Depending on the stage of the heart failure ECG-changes may be subtle and neither sensitive nor specific for the degree of cardiac dysfunction.[4]
Additionally, confounders like baseline artifacts, displaced or non-adherent electrodes, obesity, varying thoracic morphologies and interindividual fluctuations in detecting electrical abnormalities alter the diagnostic efficiency gained out of an ECG.[4] Since many years plasma natriuretic peptide and its compounds (BNP) are the gold standard biomarkers for establishing a diagnosis of heart failure and predicting its mortality.[5] Their height has been shown to correlate well with the degree of cardiac overload and "cellular-overstretch" of cardiac myocytes.[5,6]
In 2014 Skrabal et al. showed that using segmental impedance spectroscopy and additional electrodes could not only predict BNP, extracellular fluid, but also warrant a diagnosis of heart failure during the routine-ECG.[6]
In our study, we aimed to further investigate the capability of segmental impedance spectroscopy using the Combyn™ ECG to assess the data mentioned above.

1.2 Definition, terminology and classifications of heart failure

1.2.1 Definition

HF represents a clinical syndrome with varying pathophysiology and distinct etiologies rendering its definition more complex than in diseases with access to a gold standard test for the establishment of a diagnosis.[7]
Several HF societies all around the globe have published numerous HF definition to finally define this clinical syndrome, each with different centers of gravity (e.g.

pathophysiology, research criteria or measurement of plasma natriuretic peptides).[7]

Although the diagnostic criteria of HF used in current clinical practice vary in some ways, they all share the following 3 key features[7]:

- Evidence of structural heart disease
- A history of symptoms that are commonly reported in HF
- Objective signs commonly seen in HF

The currently used HF definitions come from the American College of Cardiology and American Heart association (ACC/AHA), Heart Failure Association of the ESC (HFA/ESC) and Japanese Heart Failure Society (JHFS) and are summarized in Table 1.[7]

Table 1: HF definitions in contemporary clinical practice guidelines (taken by Bozkurt et. al[7])

ACC/AHA (2013	HF is a complex clinical syndrome that results from and structural or functional impairment of ventricular filling or ejection of blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primary of edema, dyspnea, or fatigue.
ESC (2016)	HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.
JHFS (2017)	HF is a clinical syndrome consisting of dyspnea, malaise, swelling and/or decreased exercise capacity due to the loss of compensation for cardiac pumping function due to structural and/or functional abnormalities of the heart.

The predominant symptom leading to a compromise in activities of daily life varies from patient to patient.[8] Some present with a chief complaint of exercise intolerance, with hardly any evidence of fluid overload, whereas others primarily exhibit signs of an increase in extracellular volume like peripheral edema or abdominal swelling secondary to ascites formation.[8] Due to the lack of signs and symptoms of fluid overload in a substantial amount of patients the term "congestive heart failure" should not be used anymore.[8] The two leading manifestations are dyspnea and fatigue, fairly unspecific symptoms, which can be caused by many other disease processes.[8] A overview of signs and symptoms provides table 2.

Table 2: Signs and Symptoms of HF (taken from Bozkurt et. al[7])

	More specific	**Less specific**
Symptoms of HF	• Breathlessness • Orthopnea • Paroxysmal nocturnal dyspnea • Reduced exercise tolerance • Fatigue, tiredness • Ankle swelling • Inability to exercise • Swelling of parts of the body others than ankles • Bendopnea	• Nocturnal cough • Wheezing • Bloated feeling • Postprandial satiety • Loss of appetite • Decline in cognitive function, confusion (elderly) • Depression • Dizziness, syncope
Signs of HF	• Elevated jugular venous pressure • Third heart sound • Summation of gallop with third and fourth heart sounds • Cardiomegaly, laterally displaced apical impulse • Hepatojugular reflux • Cheyne Stokes respiration in advanced HF	• Peripheral edema (ankle, sacral, scrotal) • Pulmonary rales • Unintentional weight gain (>2kg/week) • Weight loss (in advanced HF) with muscle wasting and cachexia • Cardiac murmur • Reduced air entry and dullness to percussion at lung bases suggestive of pleural effusion • Tachycardia, irregular pulse • Tachypnea • Hepatomegaly, ascites • Cold extremities • Oliguria

		• Narrow pulse pressure

All of the HF definitions mostly focus on hemodynamic characterization, which although appropriate, due to symptom subjectivity and difficult assessment, are hard to apply in primary and nonspecialist care.[7]

Another disadvantage is the lack of inclusion of serum parameters notoriously elevated in cardiac dysfunction.[7] Raised BNP and NT-proBNP levels represent cardiac myocyte wall stress and increase in most forms of HF, whereas normal values virtually exclude myocardial burdening.[7]

In a recent consensus statement from numerous international heart failure associations Bozkurt et. al addressed the problem of significant variations in current HF definitions, their ambiguity and lacking standardization.[7]

They therefore proposed a universal comprehensive HF definition with clinical utility, subclassifications, prognostic and therapeutic implications and adequate sensitivity and specificity.[7]

Universal definition of HF:

- Symptoms and/or signs (Table 2) caused by structural and/or functional cardiac abnormality (as determined by an EF <50%, abnormal cardiac chamber enlargement, E/E´of > 15, moderate/severe ventricular hypertrophy or moderate/severe valvular obstructive or regurgitant lesion)
- Additionally, at least one of the following:
  - Elevated natriuretic peptide levels

Table 3: Cut-off values for natriuretic peptide levels (taken from Bozkurt et. al[7])

	Ambulatory	Hospitalized/decompensated
BNP, pg/ml	≥ 35	≥ 100
NT-proBNP, pg/ml	≥ 125	≥ 300

  - Objective evidence of cardiogenic pulmonary or systemic congestion by diagnostic modalities, such as imaging (e.g. by chest radiograph or elevated filling pressures by echocardiography) or hemodynamic measurement (e.g. right heart catheterization, pulmonary artery catheter) at rest or with provocation (exercise).

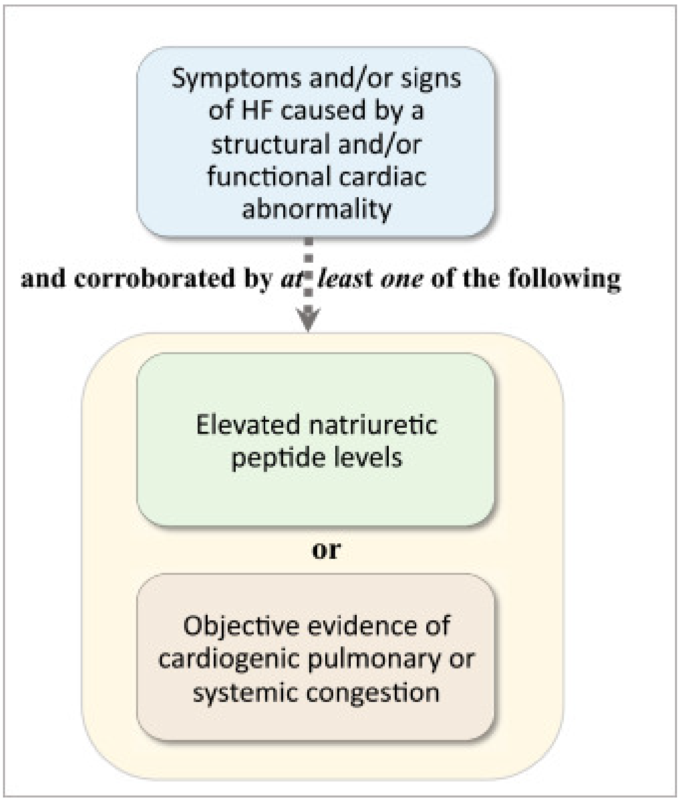


Figure 1: Universal definition of HF (taken from Bozkurt et. al[7])

It is important for clinicians to keep in mind that there is no single diagnostic test for diagnosing heart failure and it mainly remains a clinical diagnosis, supported by a carefully taken history and a precise clinical examination.[8]
Heart failure has numerous causes, nevertheless most of them can be broken down to an impairment of left ventricular function.[8]
Morphologic changes seen on echocardiography in patients with left ventricular dysfunction really are extensive ranging from normal sized ventricles with preserved ejection fraction to severely dilated cardiac chambers with a strikingly reduced ejection fraction.[8] Many predisposing conditions (e.g. hypertension, diabetes, etc.) lead to a combination of both, systolic and diastolic dysfunction, which further complicates heart failure categorization.[8]
Nowadays measurement of left ventricular ejection fraction (LVEF) has become a cornerstone of determining left ventricular systolic function.[9]

LVEF-calculation: [9]

$$LVEF = \frac{EDV - ESV}{EDV} \times 100$$

It is important to recognize that although LVEF offers important information about the efficiency of cardiac output during systole it heavily depends on the operator's experience, method of analysis and imaging technique.[8]

1.2.2 Terminology

1.2.2.1 Terminology due to LVEF

Since many years heart failure terminology gets determined by the measurement of the LVEF.[10] Heart failure with a LVEF of ≥50% is considered heart failure with preserved ejection fraction (HFpEF), whereas a LVEF <40% is typically classified as heart failure with reduced ejection fraction (HFrEF).[10] Inbetween lays an indistinct and new category termed heart failure with mildly reduced ejection fraction (HFmrEF), defined by a LVEF of 40-49%.[11,12]
In HFrEF necrosis of cardiac myocytes primary leads to dilatation of the ventricle with consecutive stroke volume reduction, whereas in HFpEF increasing LV stiffness results in an impairment of diastolic filling and markedly elevated left atrial pressure.[13]
Individuals with HFmrEF have been shown to primarily have systolic dysfunction in addition to decreased capability of the LV to relax during diastole.[10] Results of recent studies suggest that medications used in HFrEF may have a comparable effect in patients with a LVEF between 40-49%.[11] To further underline the similarity of HFmEF to HFrEF it has been renamed from "heart failure with midrange ejection fraction" to "heart failure with mildly reduced ejection fraction"[11]
It is important to distinguish between the different types of heart failure because of varying underlying risk factors, associated co-morbidities, local distribution and therapeutic response.[10] Most clinical trials regarding heart failure investigated patients with HFrEF and medical treatments have been shown to be only affective in this patient group.[10]
Heart failure with improved ejection fraction (HFimpEF) represents a newly termed condition, in which patients have a baseline LVEF ≤40%, a ≥10-point increase from baseline LVEF and of LVEF >40% in a subsequent measurement.[7]

Table 4: Terminology of heart failure with reduced, preserved, mid-range and improved ejection fraction (taken from McDonagh et. al[11] and Bozkurt et. al[7])

Type of HF	LVEF (%)	Additional criteria
Heart failure with reduced ejection fraction (HFrEF)	≤40	+ Symptoms ± signs of HF[a]
Heart failure with mildly reduced ejection fraction (HFmrEF)	41-49[b]	+ Symptoms ± signs of HF[a]
Heart failure with preserved ejection fraction (HFpEF)	≥50	+ Symptoms ± signs of HF[a] + Objective evidence of cardial structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]
Heart failure with improved ejection fraction (HFimpEF)	≤40	+ a ≥10% point increase from baseline LVEF and a second measurement of LVEF of > 40%

[a] signs may not be present in early stages of HF (especially in HFpEF) and in optimally treated patients
[b] for the diagnosis of HFmrEF, the presence of other evidence of structural heart disease e.g. (increased LA size, LVH or echocardiographic measures of impaired LV filling) makes the diagnosis more likely
[c] for the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF

1.2.2.2 Terminology due to time course

The term heart failure classically describes a complex of signs and symptoms, nevertheless effective treatment offers many individuals a life without limitations in physical activity.[10] Proven functional compromise of the LV in patients who never developed symptomatic disease is typically classified as asymptomatic LV-dysfunction.[10]

Chronic symptomatic heart failure without a change in severity due to therapeutic management over a time course of one month is described as "stable" or "compensated".[10] In this setting even small changes in fluid volume, blood pressure or electrical activity easily overstrain the cardiac functional reserve leading to "decompensation" of the chronic heart failure.[10] This process can happen over hours to days and when associated with hospitalization typically

carries an unfavorable prognosis.[10]
New onset heart failure can have an acute (e.g. due to myocardial infarction) or subacute onset (e.g. due to viral myocarditis).[10] Signs and symptoms may disappearing after treatment or remission, but myocardial injury might persist increasing the risk for consecutive complications.[10]

1.2.3 Classifications

1.2.3.1 NYHA and ACC-AHA classification

Nowadays the New York Heart Association (NYHA) classification is most commonly used to determine the level of functional impairment due to heart failure.[10] The newer ACC-AHA classification incorporates risk factors in addition to structural abnormalities and focuses more on the development and progression of heart failure, whereas the NYHA classification only outlines the degree of symptomatic disease.[8] Unfortunately studies have shown that the severity of symptoms only rarely corresponds with the degree of LV-dysfunction, rendering the NYHA classification an inaccurate diagnostic tool.[10,14] Many patients with heart failure unconsciously decrease their physical activity leading to a lack of dyspnea or fatigue. On review of systems these individuals therefore negate typical signs and symptoms causing the physician to misjudge their degree of heart failure. Health care providers should therefore keep in mind that although prominent symptoms caused by heart failure correlate with a reduced survival rate, the risk for hospitalization and death in mildly symptomatic individuals is still immense.[10]

Table 5: NYHA functional classification of HF (taken from McMurray et. al[15])

NYHA functional classification:	
Class I	No limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation or dyspnea
Class II	Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea
Class III	Marked limitation of physical activity; comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea
Class IV	Unable to carry on any physical activity without discomfort; symptoms present at rest; if any physical activity is undertaken, discomfort is increased

Table 6: ACC-AHA Stages of HF (taken from McMurray et. al[15])

ACC-AHA Stages of Heart Failure:	
Stage A	At high risk for heart failure; no identified structural or functional abnormality; no signs or symptoms
Stage B	Developed structural heart disease that is strongly associated with the development of heart failure but without signs or symptoms
Stage C	Symptomatic heart failure associated with underlying structural heart disease
Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy

1.2.3.2 Proposed revised stages of HF

To optimize the characterization of various stages of cardiac dysfunction (from being at risk for HF to having manifest HF) Bozkurt et. al proposed in their recent consensus paper newly defined stages of the HF continuum.[7]

Based on risk factors, history, signs/symptoms of HF and objective parameters of cardiac dysfunction (imaging, blood tests) they determined 4 stages of HF:

- Stage A: At-risk for HF
- Stage B: Pre-HF
- Stage C: HF
- Stage D: Advanced HF

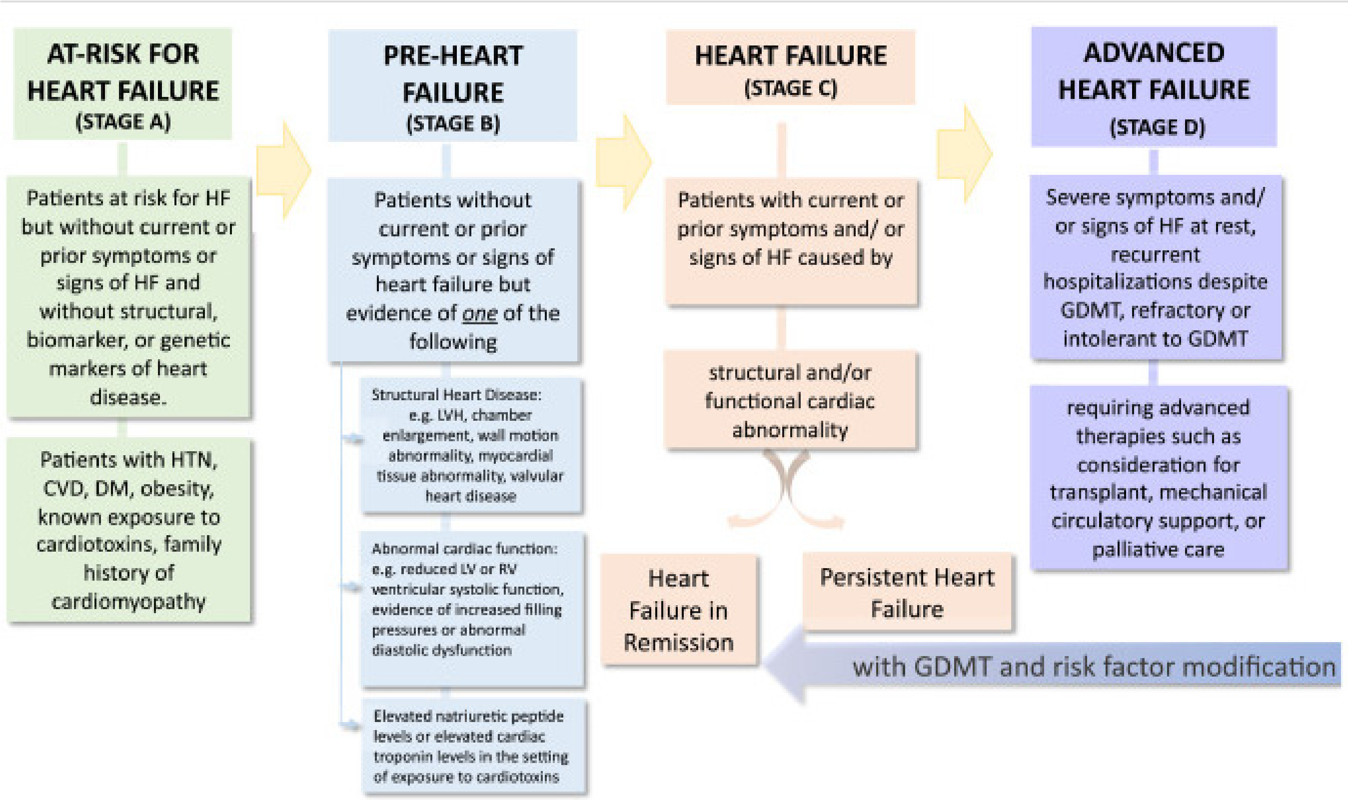


Figure 2: Stages in the development and progression of HF (taken from Bozkurt et. al[7])

1.3 Epidemiology

In recent decades chronic heart failure has become an emerging cause of morbidity and mortality affecting an amount of nearly 40 million people worldwide with an estimated prevalence of 1-2% of the adult population in developed countries, rising to over 10% in people ≥65 years.[1,3]
Even though improvements in medical management and risk factor-modification have led to a reduction in relative numbers of persons living with heart failure, absolute counts are increasing due to shifts in life expectancy and population growth.[1] Variations in socioeconomic status, ethnicity and demographics heavily influence the prevalence of heart failure globally, which makes generalized estimations inaccurate and hard to rely on.[1] Especially people with a middle- to low-income are prone to cardiovascular disease, resembling an estimated amount of 80% globally.[1]
Approximately 17% of patients presenting to primary care with dyspnea on exertion above the age of 65 will have unidentified heart failure.[10] More than 50% of patients hospitalized because of heart failure or an exacerbation of their chronic heart condition are over 75 years old.[1]
Middle aged men and women have a yearly incidence of heart failure estimated about 0,1-0,2%.[3] This rate doubles with each additional decade leading to an estimated incidence of 2-3% in individuals >85 years.[3]
The lifetime risk of heart failure in people aged 55 is higher in men (33%) than in women (28%).[10] Even though male individuals are more prone to developing cardiac disease is, longevity in females balances the prevalence between both genders.[3]
Distribution of heart failure characterized by LVEF varies between different studies, but in an analysis performed by Kapoor et al. in 2016 including 99.825 patients 49% had HFrEF, 12,8% HFmrEF and 38,1% HFpEF.[16]
Because of improvement in medical management, risk factor modification and widespread access to percutaneous coronary intervention (PCI) overall survival has improved, but mortality rate remains high with nearly 60% of individuals dying within 5 years after the diagnosis of heart failure.[1]

1.4 Etiology

Heart failure can have a whole variety of reasons ranging from congenital defects over cardiac conditions to systemic diseases.[1] Approximately 70% of cases occur as a sequela of coronary heart disease, chronic obstructive pulmonary disease (COPD), longstanding hypertension or rheumatic heart disease.[1]
The majority of patients has more than one reason for developing cardiac dysfunction and etiologies vary significantly between developed nations and low-income countries.[1] In western nations heart failure is most commonly caused by myocardial ischemia and COPD, whereas in developing countries hypertension, cardiomyopathies, myocarditis and rheumatic heart disease secondary to an undertreated streptococcal infection predominate.[1]
A great overview over the different etiologies of heart failure offer the "*2016 ESC Guidelines*" from Ponikowski et al. dividing them into conditions affecting the myocardium, abnormal loading states and arrhythmias.[10]

1.4.1 Diseased myocardium

Ischemic heart disease

Common risk factors for the development of heart failure due coronary artery disease include hypertension, hyperlipidemia, diabetes mellitus, smoking and abdominal adiposity.[1,8]
The correlation of these risk factors with a sedentary lifestyle and an unhealthy nutrition, consisting mostly of sugars and fats, is well described and explains the higher incidence and prevalence of coronary heart disease in middle- to low-income population in developed countries.[1] Further supporting this hypothesis is the high prevalence of metabolic syndrome in the US, with more than one fifth of individuals aged ≥20 and 40% aged >40 carrying this diagnosis.[8]
Ischemic heart disease accounts for roughly 70% of cases of HFrEF and seems to favor the development of HFmrEF rather than HFpEF.[12,15]
For this reason, a new diagnosis of HFrEF should usually prompt the attending physician to initiate evaluation for coronary artery disease, depending on the individual situation.

Toxic damage

Use of recreational substances like alcohol, cocaine, amphetamines or anabolic steroids, as well as exposure to heavy metal intoxications (copper, lead, cobalt, etc.) have been shown to have a direct toxic effect on cardiac myocytes.[10] Radiation- and cytostatic drug-induced cardiac toxicity, mostly from anthracyclines, is a well described side effect of antitumor therapy, although numerous other drugs have also been associated with cardiac injury, e.g. immunomodulatory agents (trastuzumab), antidepressants, antiarrhythmics, etc.[10]

Immune mediated and inflammatory damage

The most common causative agents of infectious myocarditis are viruses, mainly coxsackievirus B, adenovirus, parvovirus, human immunodeficiency virus (HIV), ebstein-barr virus (EBV), cytomegalovirus (CMV) and human herpesvirus (HHV-6), along with many others.[17] Depending on the patients demographics and exposure history additional non-viral infections should be considered, e.g. Lyme disease due to borrelia burgdorferi in the northern hemisphere and Chagas disease caused by trypanosoma cruzi in Central and South America.[17]

Noninfectious causes include autoimmune diseases like rheumatoid arthritis, connective tissue disorders (mostly systemic lupus erythematosus), hypersensitivity and eosinophilic myocarditis.[10]

Myocardial damage can occur due to a hypersensitivity reactions after the application of certain medications (e.g. anticonvulsants, antipsychotics, antibiotics) or eosinophilic infiltration of the myocardium secondary to systemic diseases associated with marked eosinophilia in the blood (helminthic infections, primary hypereosinophilic syndrome, etc.)[10,17]

Especially in cases of unexplained acute cardiac failure giant cell myocarditis is an important diagnostic consideration due to its association with a rapid decline in cardiac function, urgent need for cardiac transplantation and high mortality rate despite optimal medical treatment.[17]

Most inflammatory processes affecting the myocardium lead to heart muscle necrosis subsequently manifesting itself as dilated cardiomyopathy.[17]

Infiltration

Malignancies can directly infiltrate the myocardium or lead to metastases seeding the cardiac muscle.[10] Non-malignant causes of infiltrative disease include amyloidosis, sarcoidosis and various disorders like hemochromatosis, glycogen and lysosomal storage diseases (e.g. Pompe disease, Fabry disease).[10]

In systemic amyloidosis misfolded fibrillary proteins get deposited in various organs consecutively impairing their function.[18] Immunoglobulin light chain (AL) amyloidosis secondary to a plasma cell dyscrasia is the most common cause of myocardial amyloid infiltration and the degree of cardiac dysfunction usually determines morbidity and mortality.[18] A better prognosis warrants cardiac non-hereditary transthyretin-related amyloidosis (ATTRwt), mostly referred as senile amyloidosis.[18] In this entity myocardial buildup of misfolded transthyretin plasma proteins leads to gradual cardiac dysfunction, especially affecting older males (m:w=25-50:1).[18] It's hereditary form usually causes a systemic and peripheral neuropathy with the primary cardiac manifestations being disturbances in the cardiac conduction system.[18]

In hereditary hemochromatosis a lack of hepcidin leads to increased iron reabsorption from the gut and release from reticuloendothelial macrophages, whereas lysosomal storage diseases are caused by certain enzyme deficiencies resulting in intracellular buildup of undegradable material.[19,20]

In comparison to inflammatory conditions, most infiltrative diseases usually lead to progressive stiffening of the ventricles manifesting itself as restrictive cardiomyopathy.[18]

Metabolic derangements

Endocrine and nutritional etiologies causing heart failure are numerous. Common hormonal disturbances affecting cardiac function are hypo- as well as hyperthyroidism, parathyroid disease, diabetes mellitus and metabolic syndrome.[10] Less commonly encountered endocrinopathies include pheochromocytoma, acromegaly, hypercortisolism and pathologies associated with pregnancy and peripartum period.[10]

Heart failure can also occur because of various nutritional deficiencies.[10] Lack of thiamine (Vitamin B_1) caused by long-term drinking, digestive system disease, bariatric surgery, hyperemesis gravidarum or diuretic abuse can result in wet

beriberi.[21] This often overlooked condition usually manifests itself as unexplained heart failure with lactic acidosis, eventually even multiple organ failure with rapid improvement after thiamine repletion.[21]
Primary or secondary deficiency of the amino acid L-carnitine leads to impaired mitochondrial ß-oxidation of long-chain fatty acids.[22] Consequently cardiac myocytes lack energy supply especially during episodes of stress or starvation.[22] The introduction of carnitine supplementation therapy in 1985 made this entity a preventable and treatable cause of dilated cardiomyopathy.[22]
Additionally, decreased amounts of serum phosphate or calcium can impair cardiac function as well as a deficiency in selenium, called Keshan disease, endemic to certain parts of China.[10,23]

Genetic abnormalities

In the recent two decades there have been discovered numerous genetical mutations encoding contractional elements of the myocardium leading to phenotypical distinct entities classified as hereditary cardiomyopathies.[24]
Most of them are associated with abnormal myocardial architecture and commonly progress to debilitating cardiac dysfunction, associated with a high morbidity and mortality.[24] They get divided into hypertrophic (HCM), dilated (DCM), restrictive (RCM), leftventricular noncompaction (LVNC) and arrhythmogenic ventricular cardiomyopathy (AVC).[24]
HCM has a prevalence of 0,2% among young adults and accounts for most of the inherited cases of cardiac dysfunction.[24] It usually manifests as asymmetric or concentric myocardial thickening in the absence of risk factors or other underlying cardiac disorders and has a propensity to result in sudden cardiac death in previously healthy adolescents.[24] Hypertrophic obstructive cardiomyopathy (HOCM) accounts for about two thirds of cases and describes dynamic left ventricular outflow obstruction at rest or induced by exercise.[25] The remaining 33% display the non-obstructive form.[25] In later stages HCM usually results in combined diastolic and systolic functional impairment.[24]
More than half of all cardiomyopathies are caused by DCM, making it the most commonly encountered cardiomyopathy.[24] Based on a preexisting family history about 30-50% are classified as being hereditary in origin.[24]
Hallmarks of DCM found on imaging are dilatation of the LV and progressive

decline in stroke volume.[24] Depending on the degree of systolic dysfunction onset of symptoms varies between affected individuals and can range from early infancy to late adulthood.[24] In addition to predisposing patients to sudden cardiac death, LV-dilatation also can lead to local blood stasis and therefore increase the risk of systemic thromboembolism.[24] In many cases DCM progresses to CHF requiring heart transplantation, representing it´s most common indication.[24]

In RCM the LV becomes progressively stiff leading to impaired filling in diastole and massive atrial dilatation.[24] Adequate stroke volume is mostly maintained and myocardial thickness usually doesn't exceed normal limits.[24]

Like most inherited cardiomyopathies RCM carries an increased risk of serious cardiac-events, with a significantly low long-term survival rate.[24]

Characteristic morphologic changes seen in LVNC are hypertrabeculation of the LV apex in addition to presence of intra-trabecular recessus.[24] LVNC has been associated with various congenital heart defects and can even manifest itself as isolated right- or biventricular disease.[24]

AVC usually presents with RV dilatation, fibro-fatty myocardial changes and eventually ventricular aneursyms.[24] LV involvement is rare but possible and has recently led scientist to re-name the condition.[24] Men are more often affected than women and AVC carries an increased risk for sudden cardiac death or progression to heart failure.[24]

1.4.2 Abnormal loading conditions

Hypertension

Persistent elevations in blood pressure lead to an increase in LV myocardial mass, which can result in hypertrophy and stiffness.[1] This structural adaptation can favor the development of systolic and/or diastolic heart failure even in the absence of myocardial ischemia.[1] Long-term risk for cardiovascular accidents in patients with a blood pressure >160/90 mmHg is about twice as high as in people with values <140/90 mmHg.[1]

The Olmsted County study conducted from 2000 to 2010 in Minnesota found that hypertension is more prevalent in individuals with HFpEF, affecting 89,3% of patients, in comparison to 73,6% in patients with HFrEF.[1]

Over the last decades improvement of antihypertensive therapy has contributed a

substantial amount to the decrease of heart failure incidence, especially in the USA, where it almost halved.[1] Hypertension affects people of all demographics and many remain un-/ undertreated due to various reasons, e.g. lack of symptoms, non-compliance, insufficient treatment, etc.[1]
Results of the PURE study showed that in patients from developed countries with values >140/90 only about half of them are aware of their diagnosis, 46,7% take antihypertensive medication regularly and only 19% have appropriate blood pressure control.[1] As expected, in poorer countries these numbers seem to be even lower with 40,8%, 31,7% and 12,7%.[1]
These data clearly show the importance of early screening, effective treatment and lifelong follow-up to ensure appropriate blood pressure control to reduce global cardiovascular morbidity and mortality.[1]

Valvular and myocardial structural defects

In western nations, most cases of acquired valvular heart dysfunction are attributed to degenerative changes, whereas in developing nations rheumatic heart disease represents the predominant cause.[1] Lack of adequate antibiotic therapy of pharyngeal streptococcal infections in many of these low-income countries explains why endocardial destruction secondary to rheumatic fever still accounts for most cases of valvular HF worldwide.[1]
In the USA a dysfunctional heart valve is approximately found in one of forty people, with an estimated prevalence of over 10% in individuals older than 75 years.[1] In european countries most cases are attributed to aortic stenosis or mitral regurgitation.[26]
Additionally, infectious endocarditis, mainly caused by gram$^+$ cocci, is an important consideration in any patient with newly diagnosed valvular heart disease and signs or symptoms of systemic inflammation.[26] In recent years the number of valvular surgeries has markedly increased and represents approximately one fifth of cardiac surgeries nowadays.[26]
Lastly congenital valvular disease, atrial or ventricular septal defects can also progress to heart failure and mostly present in earlier stages of life.[10]

Pericardial and endomyocardial pathologies

In constrictive pericarditis reduced pericardial elasticity prohibits ventricular expansion during diastole leading to interventricular dependence and progressive heart failure.[27]

In developed countries most cases are attributed to prior cardiac surgery, radiation therapy or are classified as idiopathic, whereas in HIV-endemic countries tuberculosis remains the major cause.[27] Similarly pericardial effusion, depending on the rapidity of onset and amount of pericardial fluid, can limit diastolic ventricular filling resulting in reduced cardiac output.[10]

Restrictive cardiomyopathy secondary to endomyocardial fibrosis can also occur as a sequela of hypereosinophilic syndrome (termed loeffler endocarditis) or endomyocardial fibrosis (a neglected disease mostly endemic to sub-Saharan countries).[10,28]

High output states

Patients with high output heart failure typically present with dyspnea, congestion, high-normal LVEF and a hyperdynamic state, associated with elevated levels of natriuretic peptides and volume overload.[29] The various etiologies can be broken down to either reduced systemic vascular resistance (SVR) and/or increased metabolic rate.[29] Afterload reduction as a sequela of decreased SVR increases stroke volume resulting in a high LVEF.[29] Low effective arterial blood volume (EABV) triggers neurohumoral activation leading to volume retainment and expansion of extracellular volume.[29]

Disease processes associated with a decreased systemic vascular tone mostly include liver cirrhosis (reduced breakdown of vasodilatatory substances), advanced pulmonary dysfunction with hypercapnia and thiamine deficiency.[29] Shunting through larger vessels (e.g. seen in hemodialysis fistulas, Paget´s disease, hereditary hemorrhagic telangiectasia or other congenital arteriovenous malformations) can similarly lead to heart failure.[29]

Transient physiologic hyperdynamic states due to increased metabolism include inflammation and pregnancy, whereas persistent severe anemia, obesity and myeloproliferative diseases may progress to high output heart failure.[29]

Lastly sepsis and thyrotoxicosis are also important considerations, due to their high degree of morbidity and mortality.[10]

In a study with 120 participants the most common causes of high output heart failure were obesity (31%), liver disease (23%), arteriovenous shunts (23%), followed by lung disease with 16% and myeloproliferative disorders with 8%.[29] It is important to note that patients with severe anemia (Hb <8mg/dl) or thyreotoxicosis were excluded.[29]
Heart failure secondary to a hyperdynamic state carries a higher 3-year mortality rate compared to healthy individuals, especially when caused by liver failure or arteriovenous shunts.[29]

Volume overload
Renal failure or iatrogenic fluid overload rarely cause heart failure, due to widespread access to kidney replacement therapy and precise inpatient water balance.[10]

1.4.3 Arrhythmias

Disturbances in the generation of electrical signals or their conduction can lead to several rhythm abnormalities.[10]
Tachyarrhythmias can origin either from the atria or ventricles and occur due to various reasons.[10] Bradyarrhythmias are mostly caused by sinus node dysfunction or conduction disorders (e.g. atrioventricular block) and share similar etiologies.[10]
It is important to keep in mind that any rhythm abnormality, whether too fast or too slow, can when left untreated result in heart failure.[10]

1.5 Pathophysiology of heart failure

Pathophysiology of heart failure can be broken down into disturbances in systolic function, diastolic function or electrical activity.[30] These categories don´t reflect separate entities and many patients with HF have a combination of them.[30]
Risk factors for the development of HFpEF include female gender, older age, hypertension and diabetes and it´s prevalence has already overtaken HFrEF´s.[30]
Figure 3 shows the classic sequence of events in HFrEF:[30]

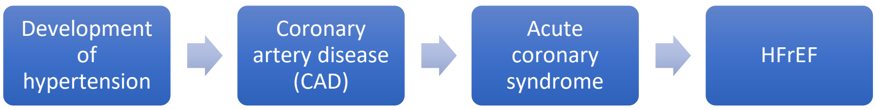


Figure 3: Pathophysiology of HFrEF (taken from Herold Innere Medizin[30])

Systolic function can be impaired due to reduced contractility (mostly caused by CAD, cardiomyopathies and myocarditis) or a rise in ventricular pressure.[30] The latter occurs secondary to increased preload caused by valvular regurgitation or increased afterload as a consequence of hypertension or valvular stenosis.[30]
Myocardial hypertrophy or impaired ventricular filling because of pericardial tamponade, restrictive cardiomyopathy or constrictive pericarditis typically results in diastolic dysfunction.[30] Lastly arrhythmias represent a separate category.[30]

1.5.1 Determinants of contractility and their changes in HFrEF

Under normal circumstances cardiac myocytes react to increased end-diastolic volume with an increase in contractility, called Frank-Starling mechanism.[30]
Currently it is hypothesized that augmented calcium sensitivity of the contractile apparatus allows cardiac myocytes to quickly adapt to changes in preload.[30]
In healthy individuals a rise in heart rate increases cardiac contractility.[30] This phenomenon is called Bowditch effect and occurs due to increased intracellular calcium concentrations.[30] Additionally activation of $ß_1$-adrenergic receptors through the sympathetic nervous system leads to positive inotropy.[30]
In HFrEF these mechanisms display a reduced effectiveness and the high concentrations of circulating adrenergic hormones result in receptor-downregulation.[30] First cardiac output diminishes only during exercise, but later on

even at rest.[30]
Diuretics are used to decrease filling pressures through diuresis, whereas cardiac glycosides have a positive impact on inotropy, mediated by increased intracellular calcium concentration.[31]
Afterload describes the pressure the heart must overcome to successfully pump blood out of the LV and therefore influences stroke volume and consecutively also contractility through changes in preload.[30] In HF neurohumoral activation leads to fluid retention and elevation in SVR resulting in increased afterload further aggravating and accelerating cardiac dysfunction.[30]

1.5.2 Determinants of ventricular filling and their changes

LV filling during diastole is a complex mechanism and determined by three variables: early-diastolic relaxation through myofilament detachment, LV stiffness influenced by structural cellular properties and configurations, as well as synchronous atrial contraction.[30]
Disturbances in any of those can therefore lead to diastolic dysfunction resulting in increased atrial pressure burden even at rest.[30] Physiologically duration of diastole shortens with a rise in heart rate.[30] Due to higher baseline filling pressures, sufficient LV filling in patients with HFpEF relies heavily on adequate diastolic duration.[30] Consequently, tachycardia decreases stroke volume and is usually poorly tolerated by patients with HFpEF.[30]

1.5.3 Pathophysiology of edema formation

Forward failure in HF is characterized by reduced cardiac output leading to systemic hypoperfusion, especially affecting the kidneys.[30] Less blood reaches the glomeruli causing decreased fluid filtration and elimination.[30] Additionally, low EABV triggers activation of RAAS and secretion of antidiuretic hormone (ADH) resulting in further Na^+- and H_20-retention.[30]
Beside these mechanisms *backward failure* also attributes to edema formation.[30]
Venous congestion leads to increased hydrostatic pressure, especially in the lower extremity, promoting fluid extravasation into the extracellular space.[30]

1.5.4. Compensatory mechanisms and therapeutic opportunities

Global hypoperfusion seen in HF results in activation of various neurohumoral pathways trying to ensure proper organ perfusion.[30] Unfortunately most of these compensatory mechanisms are only effective early on in the disease and further accelerate development of HF in later stages.[30] Most of CHF treatment therefore focuses on interrupting this vicious cycle.[30]

A reduction of the EABV leads to activation of subsequent neuroendocrine pathways.[30]

1.5.4.1 Activation of the sympathoadrenergic system

Catecholamines secreted by the adrenal medulla temporarily improve cardiac function by increasing contractility and heart rate (positive inotrope and chronotrope effects).[30] Rising levels of norepinephrine lead to downregulation of cardiac $ß_1$-adrenergic receptors, whereas blood vessels still react with an adequate constriction and vascular tone.[30] In CHF therefore sympathoadrenergic effects on the vascular system via α1-receptors predominate leading to an increase in afterload impeding with LV function.[30]

Beta blockers decrease mortality rate in patients with HFrEF.[30] They bind to $ß_1$-adrenergic receptors increasing their sensitivity to catecholamines and consecutively lessen cardiac sympathetic toxicity.[31]

1.5.4.2 Activation of the RAAS

Hypovolemia, low EABV, hyponatremia, as well as increased sympathoadrenergic stimulation through $ß_1$-adrenergic receptors trigger renin secretion by juxtaglomerular cells in the nephron, resulting in high levels of angiotensin II.[32] Binding to angiotensin type-1 receptors leads to increased systemic and renal vessel tonus (primarily of the efferent arteriole increasing glomerular filtration rate), sodium retention, stimulation of the sympathetic nervous system and salt and water craving.[32] Angiotensin II leads to ADH release by the posterior pituitary resulting in increased water reabsorption in the distal convoluted tubule and collecting duct, which further increases afterload.[30] Additionally it prompts the adrenal medulla to secrete aldosterone, which leads to increased Na^+-reabsorption and K^+-secretion in the distal convoluted tubule.[32]

Studies in rats have shown that high levels of angiotensin II and aldosterone (e.g.

seen in CHF, renal artery stenosis, etc.) likely have toxic effects on the cardiovascular and renal system.[32] Proposed mechanisms include activation of fibroblasts, increased oxidative stress and release of inflammatory cytokines resulting in tissue remodeling, progressive fibrosis and hypertrophy.[32]

Blockage of these pathways through angiotensinogen converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRA) has been shown to reduce mortality rate in patients with HFrEF.[32] Therefore these medications have become first-line treatment for individuals with HFrEF, whereas their effectiveness in HFpEF is still being investigated in various clinical trials.[32]

1.5.4.3 Release of natriuretic peptides

Cardiac natriuretic peptides include two hormones with similar structures termed atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP).[33] The former is nearly exclusively found in atrial myocytes, whereas the latter is mostly produced in ventricular myocardial cells.[33] The prohormone proBNP gets cleaved by the proteolytic enzymes furin and corin into the biologically active BNP and inactive NT-proBNP.[33,34] Stretching of cardiac myocytes represents the major stimulus for BNP secretion.[34] It´s serum levels correlate well with the degree of myocardial wall stress and can, therefore, be used to determine the stage of HF independently from clinical signs and symptoms.[33] Additional stimuli for BNP release include hormones (e.g. catecholamines, angiotensin II, etc.), as well as myocardial hypoxia, rendering higher concentrations in the setting of ACS a negative prognostic marker.[34] Under physiologic circumstances the atria represent the major source of BNP synthesis.[34] In CHF BNP-production shifts to ventricular myocytes due to increased myocardial stretch, whereas focal hypoxia and increased wall tension following ACS display similar effects.[34] Table 7 summarizes causes of elevated natriuretic peptide levels other than HF.

Physiological effects of natriuretic peptides include RAAS inhibition, diuresis and vasodilatation resulting in decreased SVR and increased renal Na^+- and H_20-excretion.[33]

Clearance of BNP occurs by binding to the natriuretic peptide clearance receptor (NPR-C) and via degradation by the neutral endopeptidase 24.11 (neprilysin).[34]

The PARADIGM-HF study by McMurray et al. published in 2014 showed that a combined inhibition of angiotensin II and neprilysin in patients with HFrEF significantly reduced morbidity and mortality in comparison to monotherapy with an ACEI and has consequently been implemented into HFrEF treatment guidelines.[30,35] Interestingly only BNP and not NT-proBNP resembles a substrate for Neprilysin and therefore angiotensin receptor neprilysin inhibitors may lead to falsely elevated BNP, but not NT-proBNP levels.[7]

NT-proBNP has a longer half-life than BNP and is therefore mostly used for diagnosing cardiac wall stress.[34] Due to its renal excretion serum levels can be inappropriately high in chronic kidney disease (CKD), although the significance of this elevation is controversial.[34] Normal plasma levels of natriuretic peptide fairly decrease the likelihood of cardiac wall stress or myocardial hypoxia.[34]

Another important diagnostic consideration for clinicians to keep in mind is that through unknown mechanisms the degree of elevation of natriuretic peptides in obese patients tends to be less pronounced than in individuals with a normal BMI.[34]

Table 7: Causes of elevated natriuretic peptide levels other than primary diagnosis of HF (taken from Bozkurt et. al[7])

Cardiovascular causes • ACS • Pulmonary embolism • Myocarditis • HCM • Valvular heart disease • Congenital heart disease • Atrial or ventricular arrhythmias
Heart contusion, cardiac infiltration or malignancy • Cardioversion, ICD shock • Pericardial disease • Invasive or surgical procedures involving the heart • Pulmonary hypertension, right ventricular failure • Infiltrative cardiomyopathies
Noncardiovascular causes • Advanced age • Kindey disease • Critical illness including sepsis syndrome, cytokine syndrome • Ischemic or hemorrhagic stroke • Pulmonary disease (Pneumonia, COPD) • Liver disease

• Severe anemia • Severe metabolic and hormone abnormalities (e.g. thyrotoxicosis, diabetic ketoacidosis, severe burns)
Causes of lower natriuretic peptide levels • Obesity/increased BMI • Pericardial disease

1.6 Deep learning and computer-aided HF detection systems

ECG is a cheap, simple, fast and non-invasive diagnostic test, which offers an immense amount of raw data and therefore represents an excellent substrate for the implementation of artificial intelligence (AI) into signal interpretation.[36] Unfortunately ECG-changes seen in HF may be very subtle and are fairly unspecific.[4] Evidence of left bundle branch block, LVH, old or new myocardial injury in addition to rhythm abnormalities can be identified and prompt further cardiac diagnostic evaluation.[37]
A normal or only mildly abnormal ECG cannot be used to rule out HF (LR- 0,27) and atrial fibrillation or new T-wave abnormalities hardly alter posttest probability (LR+ 2,2 – 3,8) of a diagnosis of HF.[37]
Additionally, various factors (electrical interference caused by insufficient electrode positioning or muscle activity, subjective interpretation and imperfect decipherment of cardiac electrical signals) reduce the sensitivity of detecting HF by visual inspection of an ECG.[4] It is therefore not surprising that establishing an accurate diagnosis of HF by manual ECG evaluation remains a serious challenge.[4]
In the last decade, many studies have been published investigating the utility of using AI to detect insufficient cardiac function by ECG signals.[4]
Combining deep learning algorithms with these so called “Computer-aided detection systems” (CADS) could offer more diagnostic certainty and render ECG a more accurate tool for diagnosing HF.[4] CADS first preprocess data, then extract distinct characteristics, followed by determination of their significance and eventually categorize them.[4]
Deep neural networks (DNNs) are a subset of AI and resemble the function and

structure of the human brain.[38] These systems learn via many layers ("therefore deep learning") of complex neural networks from input and output data.[4,38] Regarding ECG input data can be e.g. RR- and QT-intervals or QRS and T-wave morphology, whereas LVEF, rhythm and electrolyte levels represent output data.[36] Feeding a large amount of these information into the system leads to adjustments of certain network characteristics enabling it to produce model outputs as similar to the actual data.[36] The novelty of deep neural networks lies in their capability to recognize connections in the data independently of features determined by a human.[36]
Especially convolutional neural networks (CNNs) have been implemented in the analysis of routine-ECG and already partially outperform human-interpretation.[36] These deep learning algorithms work by selecting certain features by filtering data through convolutional filters and are already able to detect ECG patterns of impaired LV-systolic function, silent atrial fibrillation or HCM unidentifiable by human eyes and may even provide accurate estimations of the individual´s gender, age and electrolyte levels.[36] A downside of CNNs is that the relationship of input and output data learned by the system remains unrevealed, comparable to a black box.[36] This could reduce its clinical applicability and therefore has not yet lead to a displacement of other machine-learning systems, e.g. traditional logistic regression.[36]

In the study "*Artificial intelligence-enhanced ECG in cardiovascular disease management*" performed at the Mayo Clinic by Attia et al. ECG data of nearly 45,000 patients were fed into a CNN, which was trained to detect individuals with systolic LV dysfunction, defined by an LVEF ≤35%.[36] This system was then tested on more than 50,000 independent persons with an area under the curve (AUC), sensitivity, specificity and accuracy of 0,93, 93%, 86,3% and 85,7% respectively and was able to identify LV dysfunction before a decrease in LVEF was even measurable on echocardiography [36] Another study investigated the potential of CNN for the detection of atrial fibrillation using the sinus-rhythm ECG with an AUC of 0,87, sensitivity of 79%, specificity of 79,5% and accuracy of 79,4%.[36]
More favorable results were reached for the identification of HCM in about 600 patients and over 12,000 controls even with the usage of only one single lead (AUC 0,96, sensitivity 87% and specificity 90%).[36]

For the detection of hyperkalemia, an AI-ECG CNN was trained with more than 1,5 million ECGs of nearly 500,000 individuals, in which serum potassium levels were contemporary measured.[36] This method performed well with a sensitivity of 90% and specificity of 89%.[36]

In their recently published study "*Discovering and visualizing disease-specific ECG features using deep learning*" Van de Leur et al. investigated the ability of DNN-boosted ECG to detect and visualize ECG-changes specific to phospholamban mutation carriers.[38] In affected individuals deletion of arginine 14 in the phospholamban gene substantially increases their risk of developing a biventricular phenotype of ARVD and DCM.[38]

The DNN confirmed already established ECG-changes, identified new phospholamban mutation characteristic features and reached a sensitivity and specificity of 0,82% and 0,93%, respectively.[38]

These data demonstrate the true potential of implementing deep-learning into CADS for the detection of HF, cardiomyopathies, atrial fibrillation and even serum electrolyte levels.[4,36] Although this technology is still at an early stage it may drastically improve operating characteristics of routine ECG, revolutionize screening, diagnosis, prognosis and treatment selection in cardiovascular medicine.[36]

2 Material and Methods

In this study, we investigated the potential of detecting HF during routine-ECG using impedance plethysmography and impedance spectroscopy integrated into a 12-lead ECG, comparing the results with gold-standards e.g. NYHA-classification, ejection fraction and NT-proBNP levels.

2.1 Data source and subjects investigated

Data were obtained from 827 individuals between 16 and 97 years using the Combyn ECG™ from November 2015 to November 2020. Most measurements were conducted at the institute of cardiovascular medicine, Mariatrosterstraße 67, Graz. Between June and October 2019 data of 80 patients from the outpatient department of cardiology of the state hospital Graz, who came to their regular appointments, were obtained. The health status of the study population varied profoundly, ranging from young healthy individuals, who came in for their annual health screening, to patients with end-stage cardiovascular disease. Permission was obtained before measurement by every individual. The extracted data were deidentified and coded with consecutive numbers.

2.2 Methods

As part of a comprehensive medical history taking patients were asked to quantify the degree of their impairment in daily activity by using the NYHA classification. Blood samples were drawn from every individual to determine NT-proBNP levels. If indicated, echocardiography was performed to further detect and characterize structural and functional cardiac abnormalities. Blood pressure was measured 3 times in a row using the DINAMAP Procare 300 sphygmomanometer and according to the SPRINT-Study protocol (after a period of rest, measurement with an automated device, absence of physician during rest period and blood pressure measurement).[39]

2.3 The Combyn^{TM} ECG

The Combyn^{TM} ECG (Figure 4) represents a novel medical device that consists of a 12-lead ECG that additionally provides extensive information about the individual's cardiovascular condition and body composition. Whereas conventional ECGs only measure electrical activity, the Combyn^{TM} ECG additionally enables measurement of cardiac mechanics.

It provides a "scientific report", which includes estimations of:

- Heart mechanics
- BNP-estimation with detection of HF
- Aortic pulse wave velocity
- Detection of peripheral artery disease
- Measurement of total body water and extracellular volume
- Early detection of localized edema
- Measurement of muscle mass
- Sarcopenia grading

Figure 4: The Combyn^{TM} ECG

2.4 Impedance measurements

Before starting with the measurement, the individuals' height and weight were determined. Additionally, waist and hip circumferences, as well as arm, leg, thorax and trunk lengths were assessed with a tape measure and the data fed into the Combyn^{TM} ECG.

The subjects rested for at least 10 minutes in the supine position.[6] To alleviate dyspnea in patients with symptomatic HF the upper torso of all individuals was elevated at an angle of 30°.[6]

Electrodes were applied as shown in Figure 5 and measurements were performed.[6]

Arm and leg electrodes of the traditional ECG were replaced by double band clamp electrodes for impedance and ECG measurements.[6] Arm electrodes were positioned proximal to the wrists and leg electrodes at the ankles.[6] A pair of adhesive ECG electrodes was attached to the right side of the neck.[6]

All extremity and thoracic electrodes were moisturized with an ECG electrode spray.[6]

To assess the thoracic and abdominal segments current was passed between the outer neck and outer left leg electrodes.[6] Arms were measured between the outer neck and outer arm electrodes, legs between the outer neck and outer leg electrodes.[6] Segmental impedance measurements were performed at 5, 40 and 400 kHz at the thorax, abdomen and both legs.[6] The ratio of extracellular to intracellular water (ECF/ICF ratio) of these segments was calculated using the abovementioned impedances in addition to specific resistances of ECF and ICF.[6]

The amplitude of blood acceleration over the thorax and extremities was calculated through the heartbeat dependent volume change in the individual segment. In this study, we investigated the blood acceleration over the thorax and the left leg.

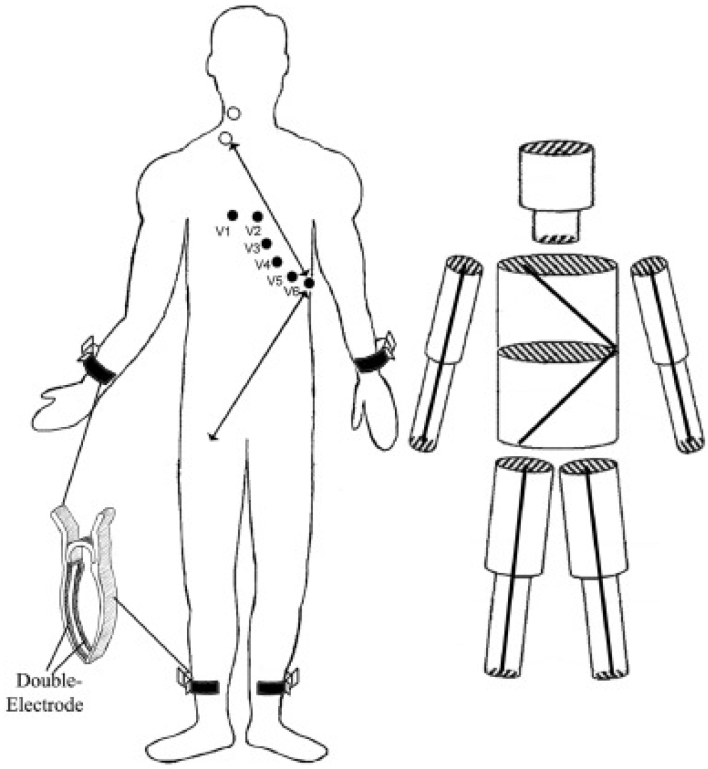


Figure 5: Electrode placement (taken from Skrabal et. al[6])
Placement of the electrodes for the impedance measurements correspond to the placement of the conventional 12-lead ECG with one additional double electrode at the right side of the neck. Thorax and abdomen are measured diagonally between the inner neck electrode and V6, and between V6 and the right groin. The resulting 6-cylinder-model is shown on the right.

2.5 Statistical analysis

The data collected was prepared prior to starting the statistical analysis. Due to the sheer amount of data certain filters were applied to only select measurements with the information required for this study (NT-proBNP levels, NYHA functional class, ECV/ICV-ratio, pulse wave acceleration, etc.).
Afterwards the dataset was analyzed using the statistical software program SPSS. Exploratory data analysis was conducted to investigate the distribution characteristics of the data. Kruskal-Wallis test was used for comparison of the subgroup and chi-square testing for the categorical values. Pearson correlation coefficient was used to estimate the correlation between the sets of data and the significance level was determined at 0.05.

3 Results

Table 8, 9 and 10 show the baseline characteristics of study participants.

Table 8: Gender distribution of study participants

Gender

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	m	459	55,5	55,5	55,5
	f	368	44,5	44,5	100,0
	Total	827	100,0	100,0	

Table 9: Baseline characteristics of male study participants

Male study participants

	Count	Mean	Standard Deviation	Median	Minimum	Maximum
Age	459	69,43	14,83	74,10	16,56	96,00
Weight	459	83,51	14,37	81,70	50,80	149,60
Height	459	175,86	7,14	175,00	159,00	198,00
BMI	459	26,99	4,31	26,20	16,22	51,99
Mean systolic BP	459	135,54	22,88	133,33	75,67	209,00
Mean diastolic BP	459	79,32	12,68	79,00	42,00	128,00
NT-proBNP	459	935,29	3465,05	275,00	5,00	55881,00
Mean of ECF/ICF of LE	459	27,84	2,61	27,76	21,48	35,11
Amplitude of BA thorax*	459	1,08	,35	1,06	,29	2,43
Amplitude of BA left leg*	459	,95	,28	,92	,23	2,40

*blood acceleration (measured in ohm)

Table 10: Baseline characteristics of female study participants

Female study participants

	Count	Mean	Standard Deviation	Median	Minimum	Maximum
Age	368	68,40	15,13	73,33	18,44	97,20
Weight	368	67,98	12,87	65,40	46,50	121,20
Height	368	163,58	6,67	165,00	141,00	178,00
BMI	368	25,43	4,79	24,16	17,19	49,17
Mean systolic BP	368	139,62	24,41	139,33	66,67	241,67
Mean diastolic BP	368	82,30	13,80	81,00	31,67	129,00
NT-proBNP	368	664,08	1407,41	193,00	5,00	16679,00
Mean of ECF/ICF of LE	368	28,10	2,15	27,88	21,98	34,26
Amplitude of BA thorax*	368	1,52	,59	1,50	,33	3,23

Amplitude of BA left leg*	368	1,10	,27	1,09	,28	2,04

*blood acceleration (measured in ohm)

Measured serum-NT-proBNP levels were divided into 4 classes:

- 1 ≤125 pg/ml
- 2 125 pg/ml - 400 pg/ml
- 3 401 pg/ml - 1000 pg/ml
- 4 > 1000 pg/ml

Table 11: NT-proBNP-levels in serum

NT-proBNP serum classes (1 - 4)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1,00	269	32,5	32,5	32,5
	2,00	255	30,8	30,8	63,4
	3,00	140	16,9	16,9	80,3
	4,00	163	19,7	19,7	100,0
	Total	827	100,0	100,0	

Additionally, the Combyn™ ECG estimated through discriminant analysis, established by intellectual property, 4 classes of Heart function.

<u>Heart function by Combyn™ ECG classes:</u>

- Class 1: no HF
- Class 2: mild HF
- Class 3: moderate HF
- Class 4: severe HF

Table 12: Heart function by Combyn™ ECG

Heart function by Combyn ECG

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1,00	137	16,6	16,6	16,6
	2,00	289	34,9	34,9	51,5
	3,00	200	24,2	24,2	75,7
	4,00	201	24,3	24,3	100,0
	Total	827	100,0	100,0	

3.1 Comparison of heart function by Combyn^{TM} ECG with serum NT-proBNP levels

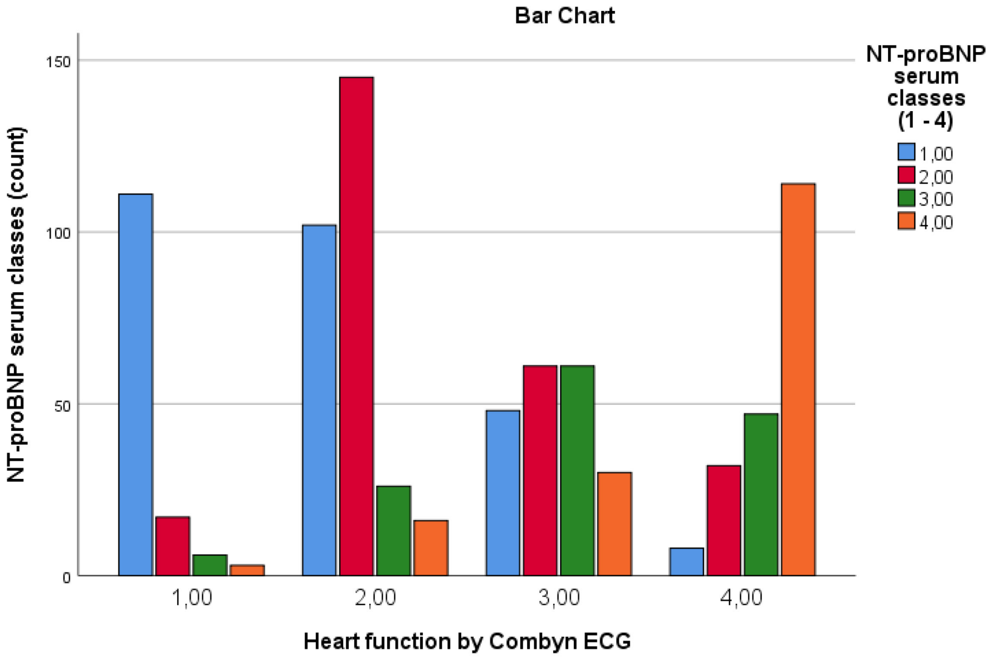


Figure 6: Bar chart of heart function by Combyn^{TM} ECG and serum NT-proBNP classes 1 to 4

Crosstabulation was performed and the pearson chi-square test showed a p-value <0,001, revealing a significant association between NT-proBNP-levels and heart function. Because of the not normally distributed metric values of NT-proBNP a Kruskal-Wallis-test was performed (p-value <0.001). Additionally, pairwise comparisons of heart function by Combyn^{TM} ECG all displayed a p-value <0.001, signaling significant differences between the classes.

Strong effect sizes were reached with the comparison of class 1 with class 3 and 4 and class 2 with class 4. Effect sizes were moderate, when comparing class 1 with class 2, as well as class 3 with class 4 and weak for the comparison of class 2 with class 3.

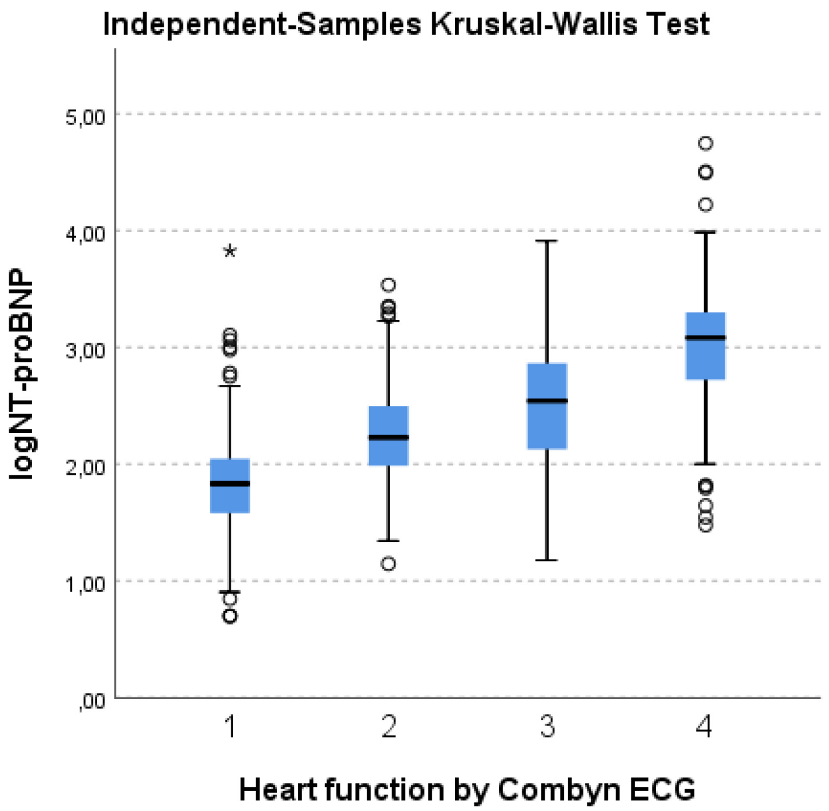
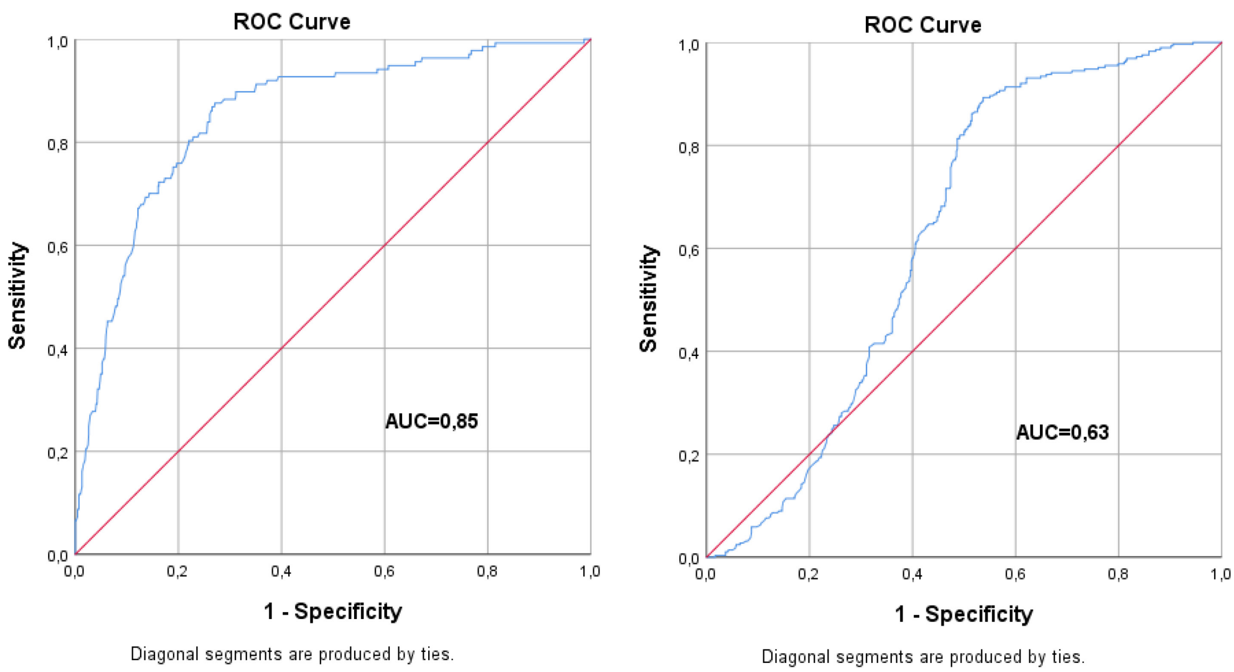
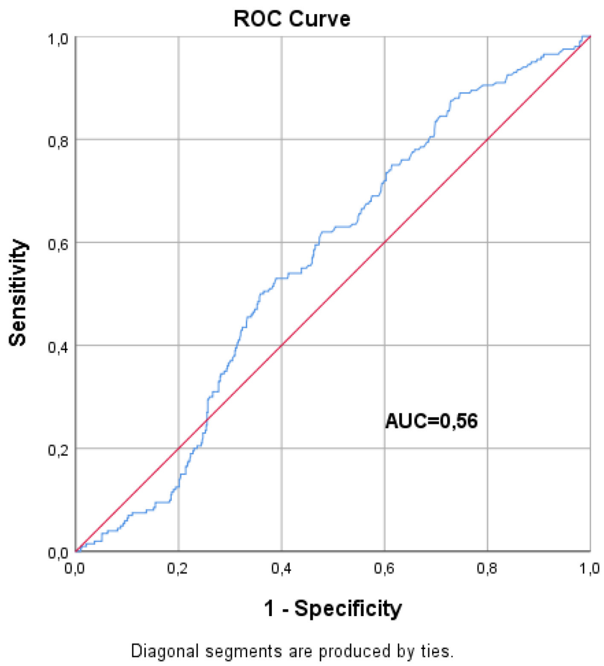
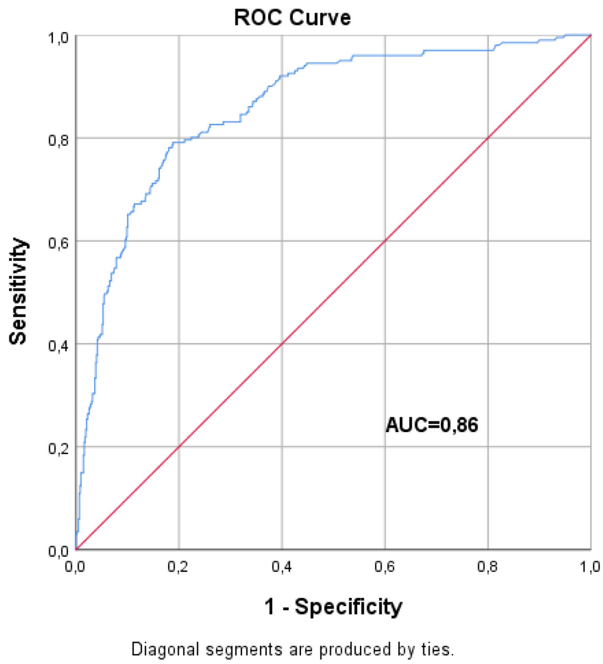


Figure 7: Kruskal-Wallis test of logNT-proBNP and heart function by Combyn^{TM} ECG



Figures 8 and 9: ROC-Curves of NT-proBNP-classes for heart function by Combyn^{TM} ECG 1 and 2





Figures 10 and 11: ROC-Curves of NT-proBNP-classes for heart function by Combyn^{TM} ECG 3 and 4

ROC-curves (receiver operating characteristics) are shown above and AUCs display the following results: 0.85, 0.63, 0.56 and 0.86 respectively for the serum NT-proBNP-classes 1 to 4.

3.2 Comparison of Heart function by Combyn^{TM} ECG with NYHA classification

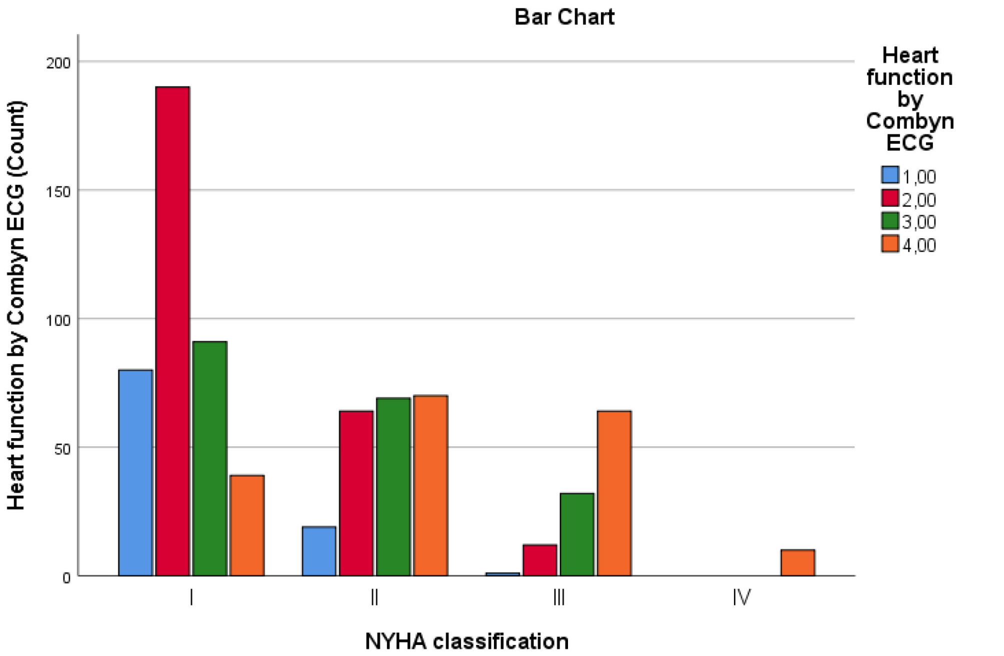


Figure 12: Bar chart of NYHA classification and heart function by Combyn^{TM} ECG

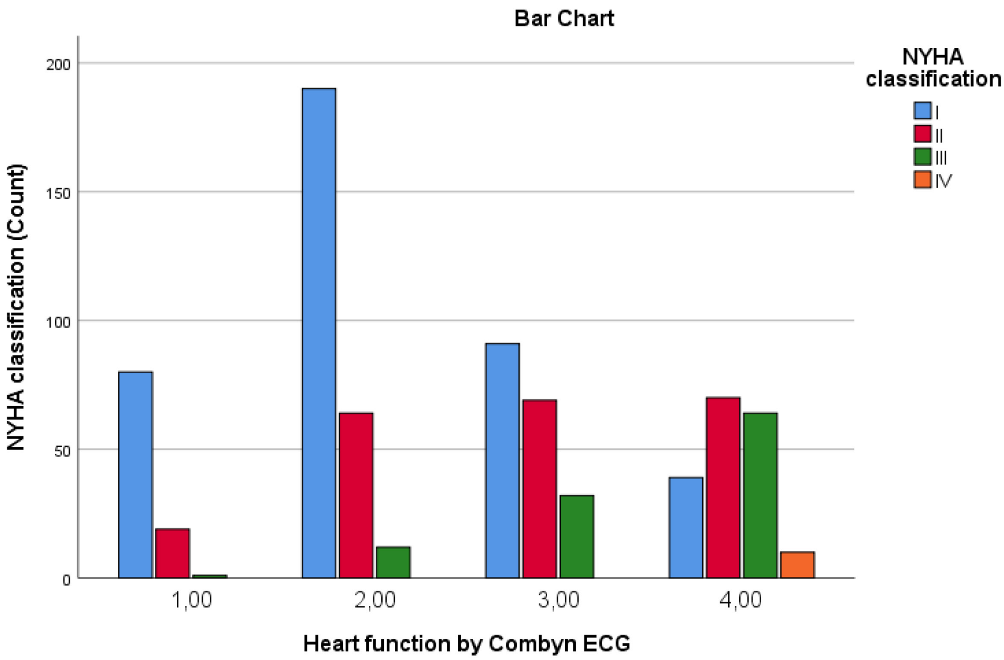
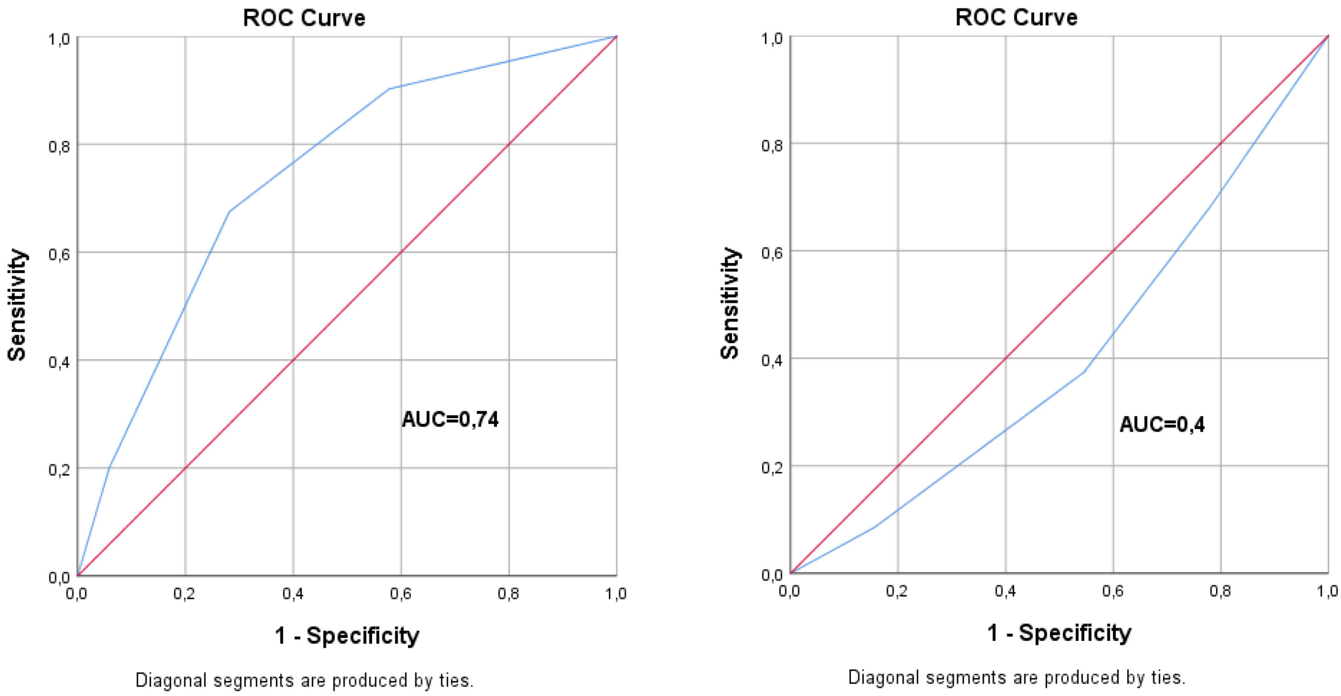
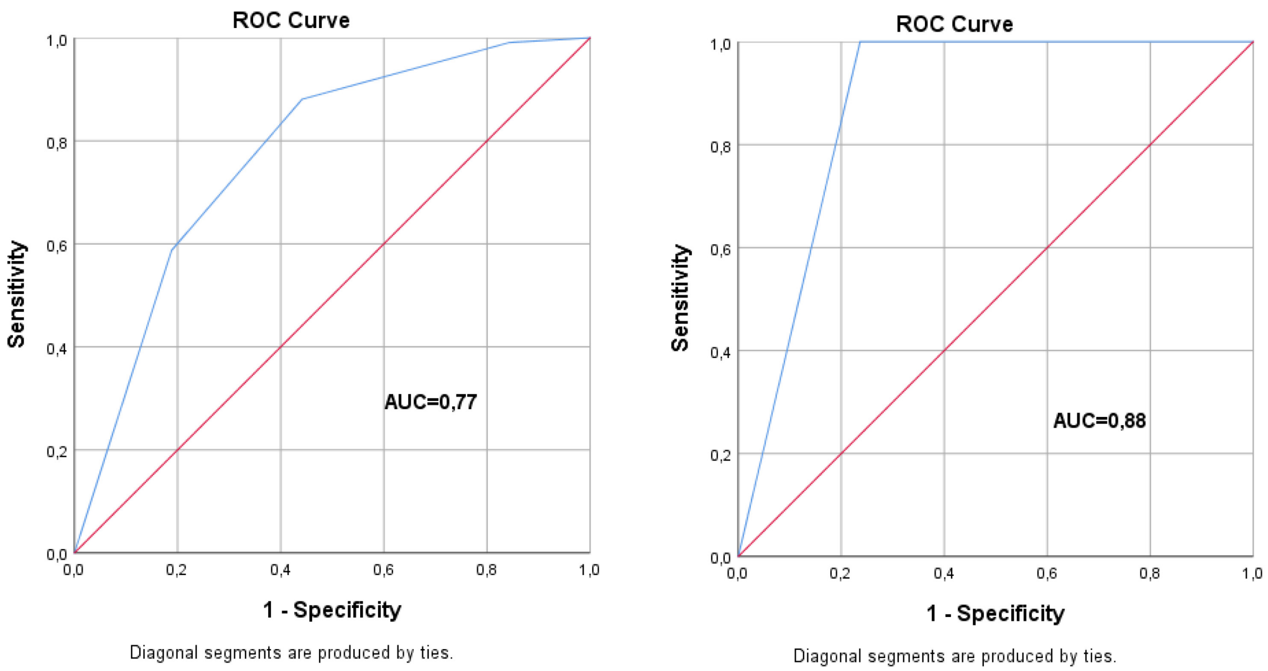


Figure 13: Bar chart of heart function by Combyn^{TM} ECG and NYHA classification

Crosstabulation was performed and the pearson chi-square test showed a p-value <0,001, revealing a significant association between NYHA-classification and heart function by Combyn^{TM} ECG.



Figures 14 and 15: ROC-Curves of NYHA-classification for heart function by Combyn^{TM} ECG I and II



Figures 16 and 17: ROC-Curves of NYHA-classification for heart function by Combyn^{TM} ECG III and IV

ROC-curves are shown above and AUCs display the following results: 0.74, 0.4, 0.77 and 0.88 respectively for signs and symptoms of HF using the NYHA-classification 1 to 4.

3.3 Comparison of serum NT-proBNP levels with NYHA classification

Table 13: NT-proBNP levels across NYHA classification classes

		NT-proBNP levels					
		Count	Mean	Standard Deviation	Median	Minimum	Maximum
NYHA classification	1,00	400	285,99	470,36	137,50	5,00	5197,00
	2,00	222	1036,71	3096,09	440,00	11,00	32000,00
	3,00	109	2190,05	5424,25	1411,00	62,00	55881,00
	4,00	10	5318,50	4765,79	4404,00	1013,00	16679,00

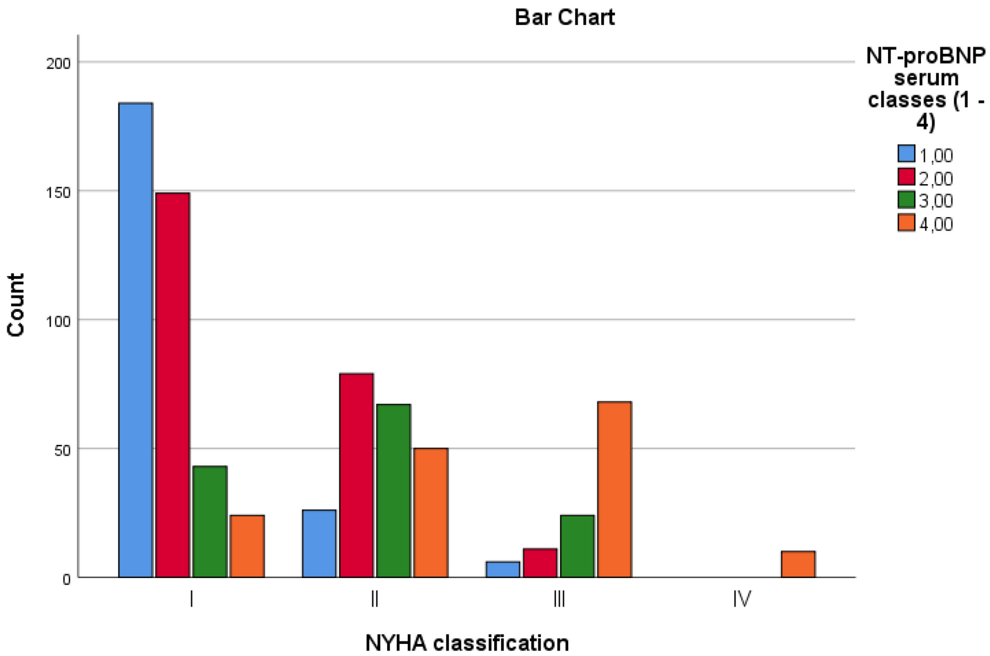


Figure 18: Bar chart of NYHA classification and serum NT-proBNP classes

Crosstabulation was performed and the pearson chi-square test showed a p-value <0,001, revealing a significant association between NT-proBNP-levels and NYHA classification. Because of the not normally distributed metric values of NT-proBNP a Kruskal-Wallis-test was performed (p-value <0.001). Additionally, pairwise comparisons of NYHA classification all displayed a p-value <0.001, signaling significant differences between the NYHA classification groups, except for the comparison of class 3 with class 4.

Effect sizes were strong for the comparison of class 1 with class 3, moderate for the comparison of class 1 with class 2 and 4 and weak for the comparison of class 2 with class 3 and 4.

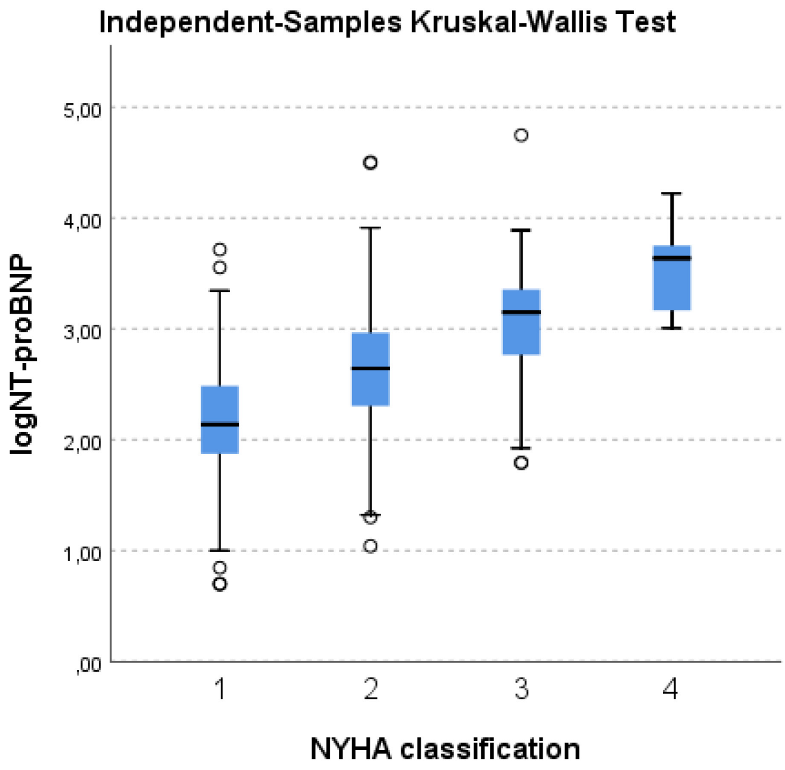
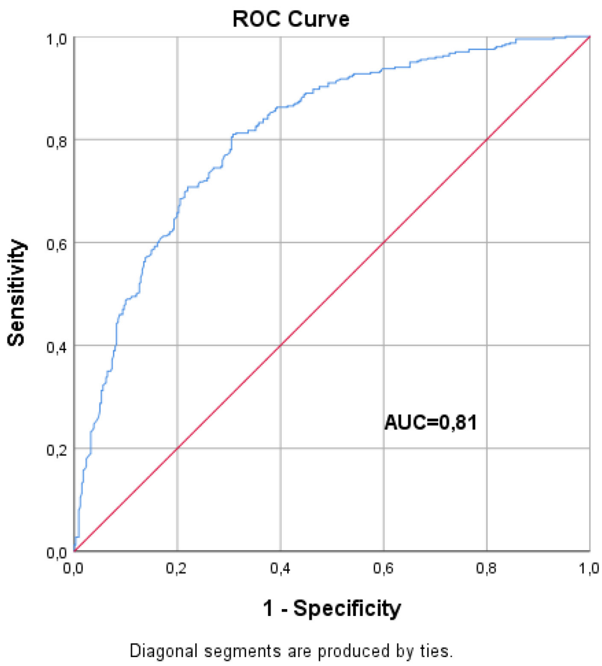
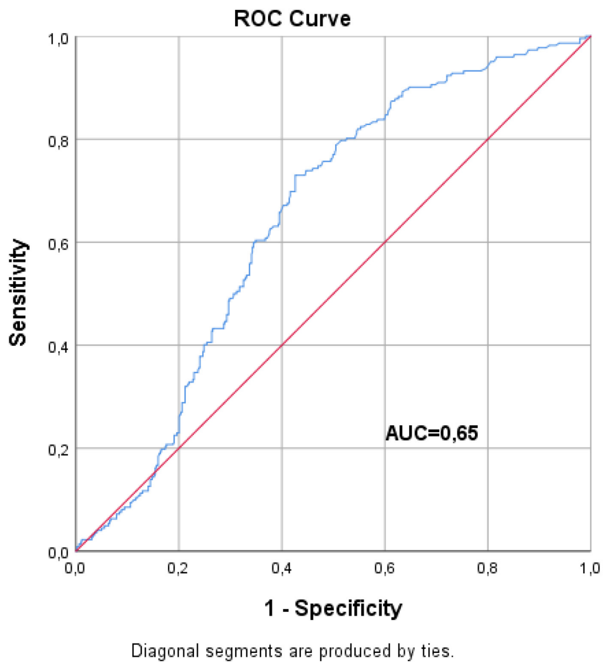
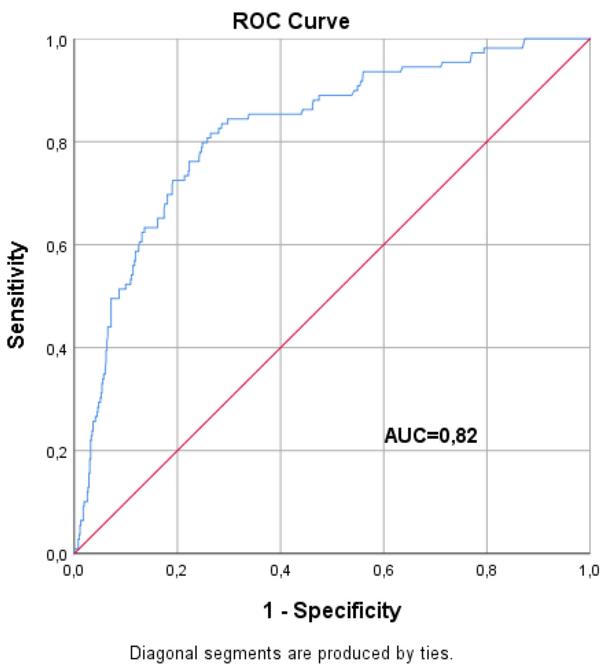


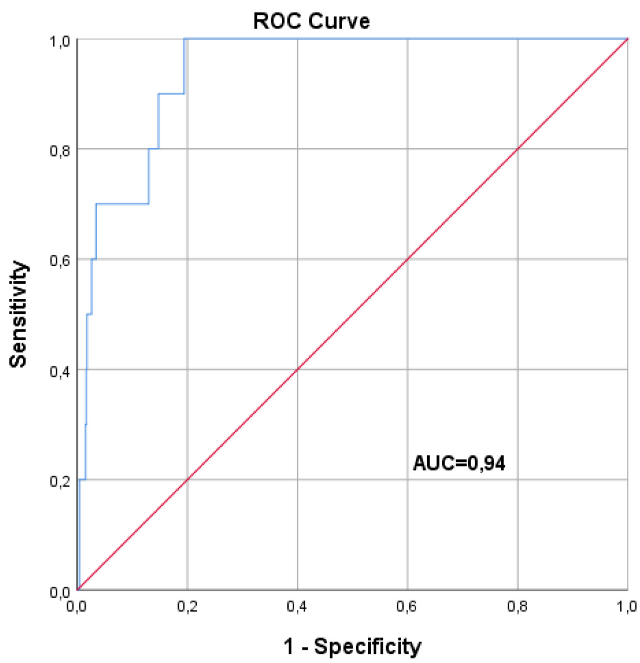
Figure 19: Kruskal-Wallis test of logNT-proBNP and NYHA classification I – IV





Figures 20 and 21: ROC-Curves of NT-proBNP-levels for NYHA classes I and II





Figures 22 and 23: ROC-Curves of NT-proBNP-levels for NYHA classes III and IV

ROC-curves are shown above and AUCs display the following results: 0.81, 0.65, 0.82 and 0.94, respectively for the NYHA functional classes.

3.4 Comparison of Heart function by Combyn^{TM} ECG with ECF/ICF ratio in lower extremities

Because of the not normally distributed values of ECF/ICF mean of right and left lower extremity a Kruskal-Wallis-test was performed (p-value <0.001). Additionally, pairwise comparisons of heart function all displayed a p-value <0.001, signaling significant differences between the heart function by Combyn^{TM} ECG classes.

Effect sizes were strong when comparing class 1 with class 2, 3 and 4. The comparison of class 2 with 4 and class 3 with 4 revealed moderate effect sizes and a weak effect size for class 2 with class 3.

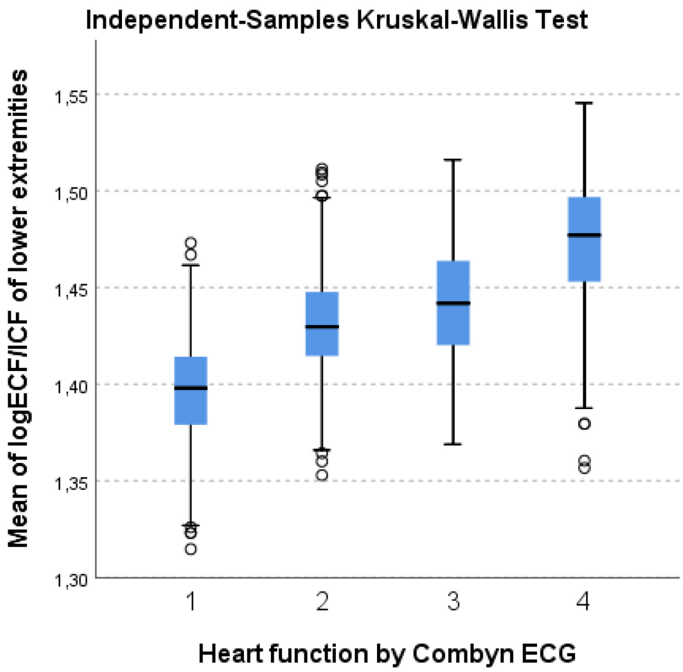
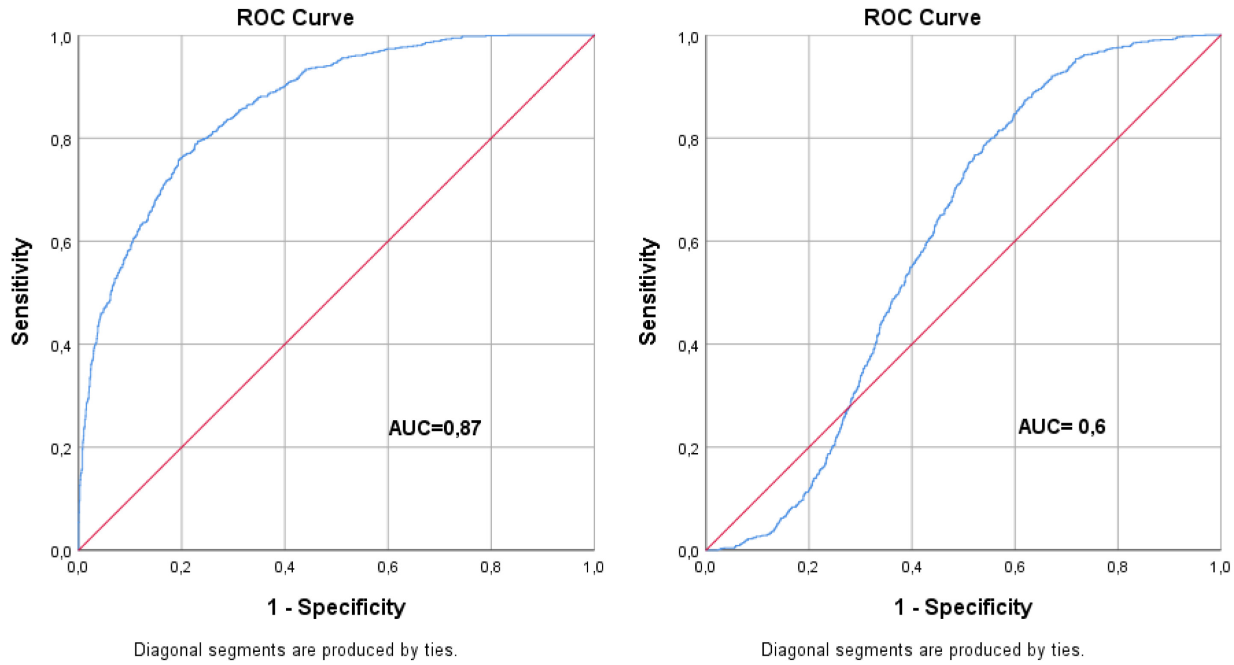
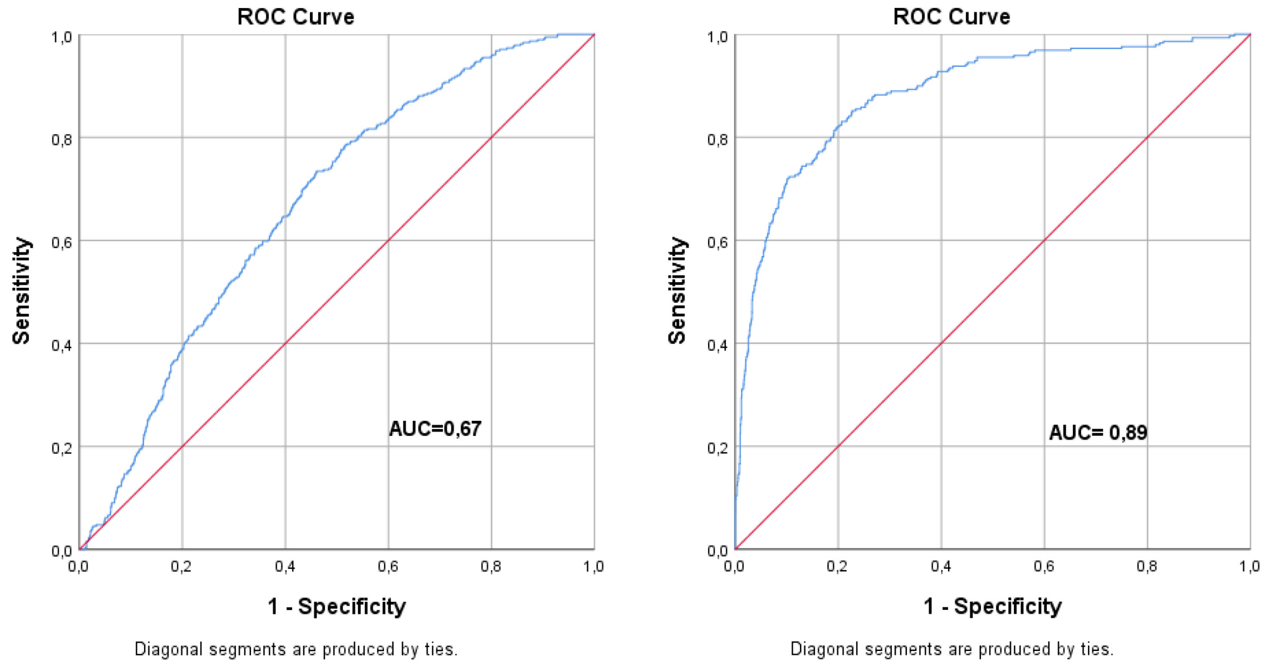


Figure 24: Kruskal-Wallis test of mean of logECF/ICF of lower extremities and Heart function by Combyn^{TM} ECG



Figures 25 and 26: ROC-Curves of mean of ECF/ICF of lower extremities for Heart function by Combyn™ ECG 1 and 2



Figures 27 and 28: ROC-Curves of mean of ECF/ICF of lower extremities for Heart function by Combyn™ ECG 3 and 4

ROC-curves are shown above and AUCs display the following results: 0.87, 0.6, 0.67 and 0.89, respectively for the mean of ECF/ICF of lower extremities.

3.5 Comparison of Heart function by Combyn^{TM} ECG with the amplitude of blood acceleration over the thorax

Because of the not normally distributed values of amplitude of blood acceleration in the thorax a Kruskal-Wallis-test was performed (p-value <0.001). Additionally, pairwise comparisons of heart function all displayed a p-value <0.001, signaling significant differences between the heart function by Combyn^{TM} ECG classes, except for the comparison of class 1 with class 2 and class 3 with class 4.
Effect sizes were all strong (class 1 with class 3 and 4, class 2 with class 3 and 4).

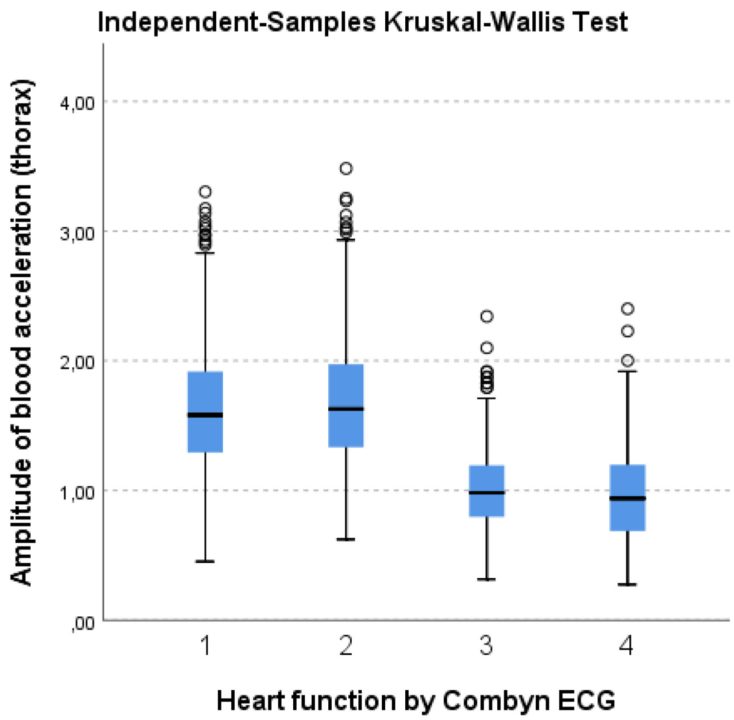
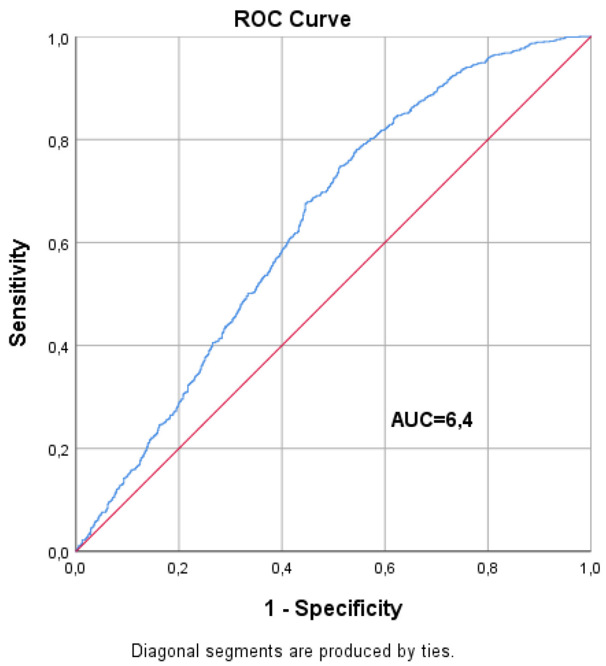
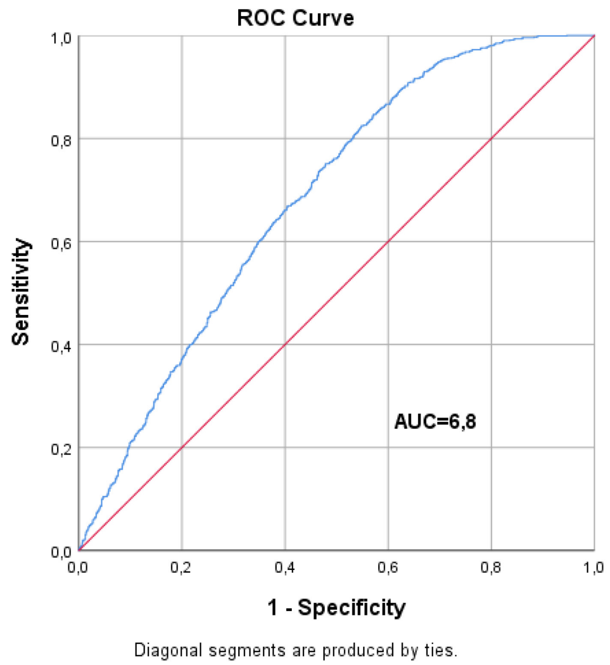
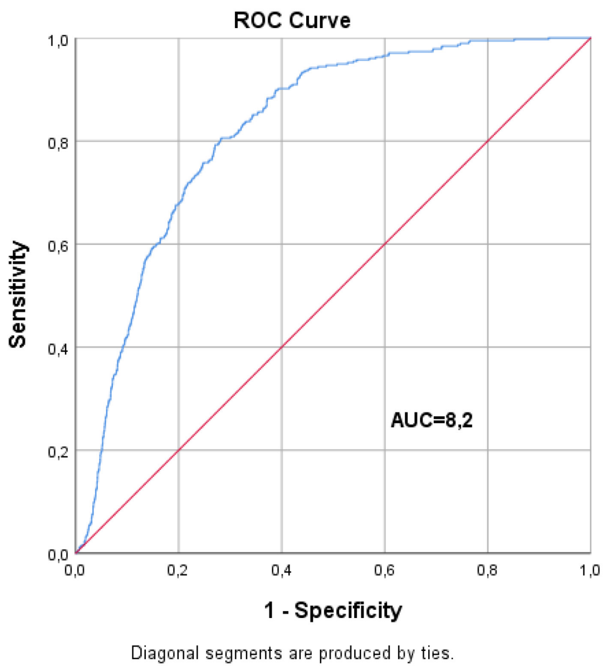


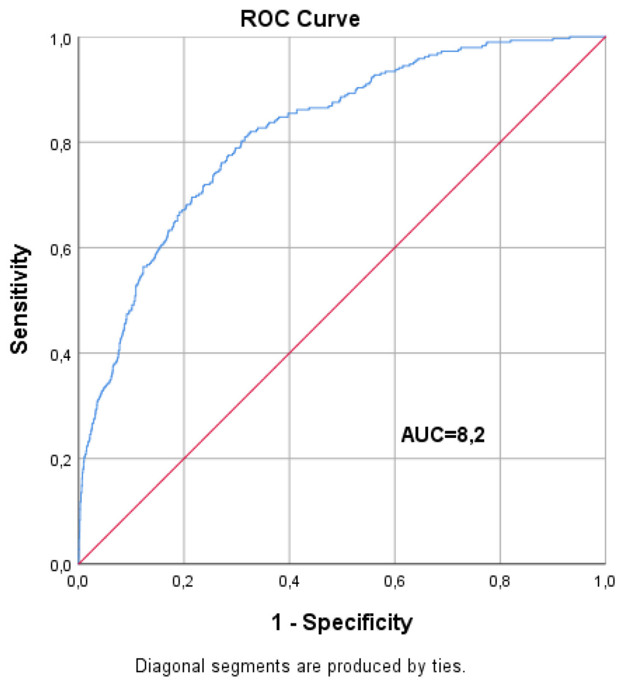
Figure 29: Kruskal-Wallis test of amplitude of blood acceleration in the thorax and heart function by Combyn^{TM} ECG





Figures 30 and 31: ROC-Curves of blood acceleration in the thorax for heart function by Combyn™ ECG 1 and 2





Figures 32 and 33: ROC-Curves of blood acceleration in the thorax for heart function by Combyn™ ECG 3 and 4

ROC-curves are shown above and AUCs display the following results: 0.64, 0.68, 0.82 and 0.82, respectively for the amplitude of blood acceleration over the thorax.

3.6. Comparison of Heart function by Combyn™ ECG with the amplitude of blood acceleration over the left leg

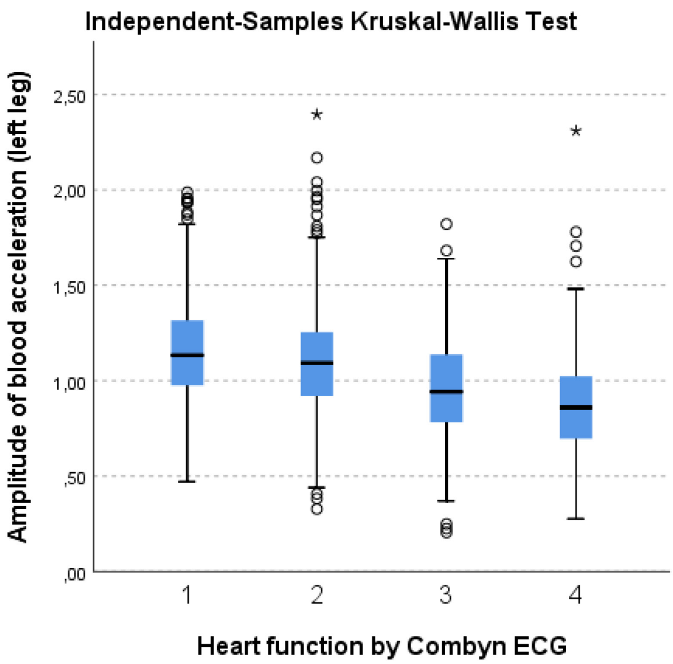
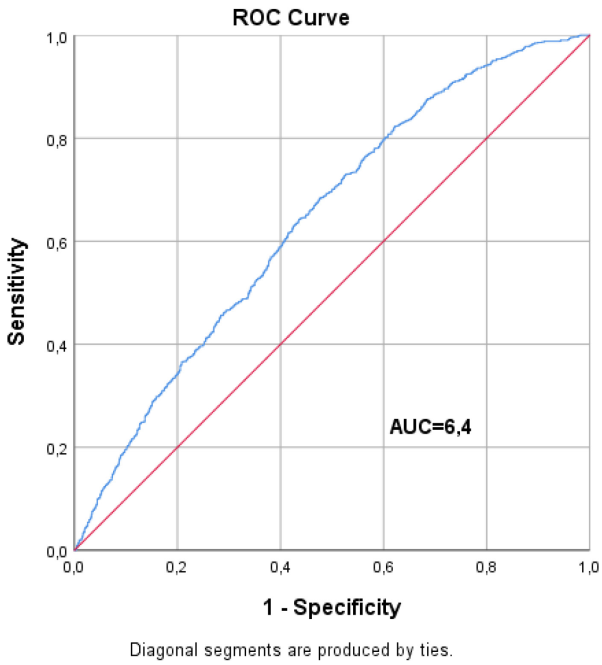
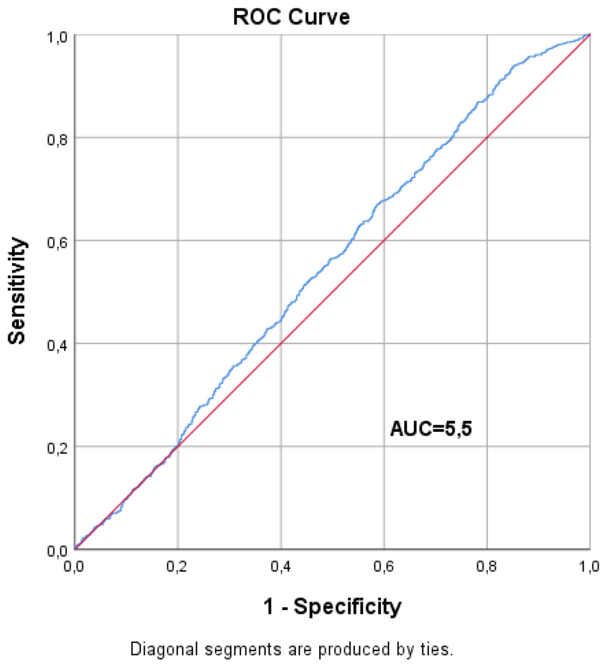


Figure 34: Kruskal-Wallis test of amplitude of blood acceleration in the left leg and heart function by Combyn™ ECG

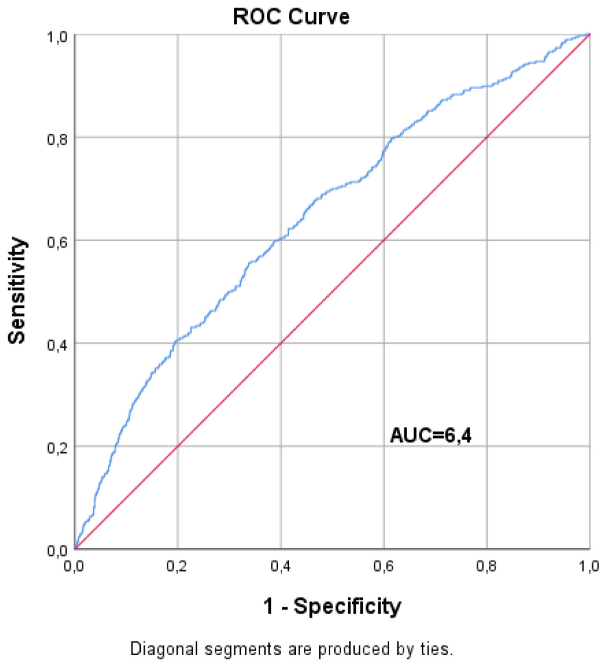
Because of the not normally distributed values of amplitude of blood acceleration over the left leg a Kruskal-Wallis-test was performed (p-value <0.001). Additionally, pairwise comparisons of heart function all displayed a p-value <0.001, signaling significant differences between the heart function by Combyn™ ECG classes.

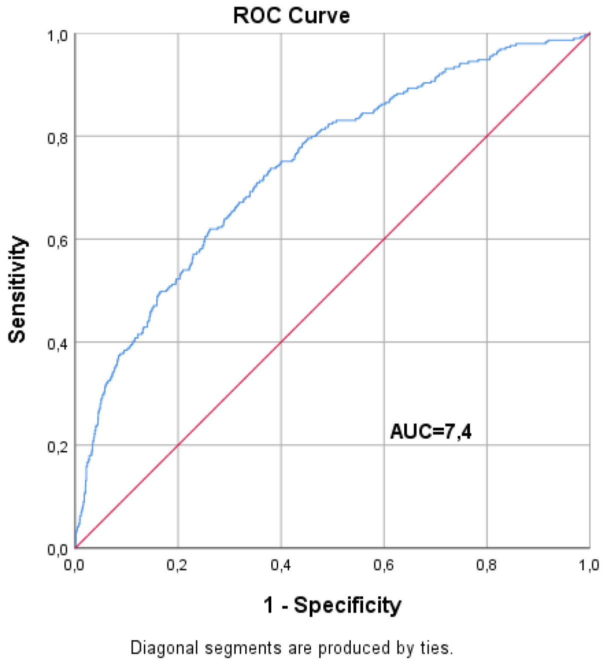
Effect sizes were moderate for the comparison of class 1 with class 3 and 4 and class 2 with class 4 and weak when comparing class 1 with class 2 and class 2 with class 3.





Figures 35 and 36: ROC-Curves of blood acceleration in the left leg for heart function by Combyn^{TM} ECG 1 and 2





Figures 37 and 38: ROC-Curves of blood acceleration in the left leg for heart function by Combyn^{TM} ECG 3 and 4

ROC-curves are shown above and AUCs display the following results: 0.64, 0.55, 0.64 and 0.74, respectively for the amplitude of blood acceleration over the left leg.

4. Discussion

As already discussed above, integrating artificial intelligence into ecg-interpretation could markedly improve diagnostic yield and provide numerous additional data on the individuals cardiovascular and general health.
With the implementation of segmental impedance spectroscopy and plethysmography into measurements the Combyn^{TM} ECG represents a novel medical device that offers innumerable informations about cardiovascular function and body composition.
In their work from 2014 *"Adding hemodynamic and fluid leads to the ECG. Part I: The electrical estimation of BNP, chronic heart failure and extracellular fluid accumulation"* Skrabal et. al layed the foundation for this present study.
With the measurement of blood acceleration, volume change in the thorax and both legs with each heart beat and reliable detection of fluid overload they reached an AUC of 0,93 for the predicted plasma NT-proBNP of >400 pg/ml.[6]
In our study, we further investigated the accuracy, sensitivity and specificity of the Combyn^{TM} ECG to detect cardiac dysfunction and HF. We did this by analyzing and correlating the estimated heart function (calculated by the Combyn^{TM} ECG) with objective (e.g. NT-proBNP levels), as well as subjective (NYHA classification) HF parameters.

4.1 Heart function by Combyn^{TM} ECG and NT-proBNP

Comparing the heart function by Combyn^{TM} ECG and serum NT-proBNP classes (1 ≤125 pg/ml, 2 between 125 - 400 pg/ml, 3 between 401 - 1000 pg/ml and 4 > 1000 pg/ml) revealed a significant relationship between the same classes.
The Combyn^{TM} ECG reached a satisfying accuracy for the detection of patients with a NT-proBNP ≤125 pg/ml of 0,85% and individuals with a NT-proBNP >1000 pg/ml of 0,86%, respectively.
In the Heart function by Combyn^{TM} ECG class 1 81% (n=111) of patients had NT-proBNP levels ≤125 pg/ml, 12.4% (n=17) between 125 - 400 pg/ml, 4.4% (n=6) between 401 - 1000 pg/ml and only 2.2% (n=3) levels >1000 pg/ml.
In contrast in the class with NT-proBNP levels ≤125 pg/ml 41.3% (n=111) of patients were classified as Heart function 1, 37.9% (n=102) as Heart function 2, 17.8% (n=48) as Heart function 3 and only 3% (n=8) as Heart function 4.

In the Heart function class 2 35.3% (n=102) of individuals were in the NT-proBNP serum class 1, 50.2% (n=145) in serum class 2, 9% (n=26) in serum class 3 and 5.5% (n=16) in serum class 4.
Distribution of NT-proBNP serum classes in Heart function class 3 was as follows: 24% (n=48), 30,5% (n=61), 30,5 (n=61) and 15% (n=30) for the serum classes 1 - 4, respectively.
In the group with NT-proBNP levels > 1000 pg/ml 69.9% (n=114) of study participants were staged as Heart function 4, 18.4% (n=30) as Heart function 3, 9,8% (n=16) as Heart function 2 and 1.8% (n=3) as Heart function 1.
The Heart function by Combyn™ ECG group 4 consisted of 4% (n=8) with NT-proBNP levels ≤125 pg/ml, 15.9% (n=32) between 125 - 400 pg/ml, 23.4% (n=47) between 401 - 1000 pg/ml and 56.7% (n=114) levels > 1000 pg/ml.
Additionally, pairwise comparisons of the Heart function by Combyn™ ECG classes were performed and showed significant differences between every single one of them.
The Kruskal-Wallis test revealed that the Combyn™ ECG performs well classifying and labeling patients correctly with low or very high NT-proBNP levels (strong effect sizes for the comparison of class 1 with class 3 and 4 and class 2 with class 4). In contrast effect sizes were lower when comparing adjacent groups (moderate for the comparison of class 1 with 2 and class 3 with 4 and weak for the comparison of class 2 with 3).
These data show that the Combyn™ ECG represents a reliable tool for the distinction and detection of patients with high and low NT-proBNP levels and can therefore provide quick important information about the degree of the individual´s cardiac load to further guide clinical decision making.

4.2 Heart function by Combyn™ ECG and NYHA classification

Comparison of Heart function by Combyn™ ECG and NYHA classification revealed a significant association between the corresponding classes. ROC curves of NYHA-classification displayed AUCs of 0.74, 0.4, 0.77 and 0.88 for Heart function groups 1 – 4 by Combyn™ ECG, respectively. These data show that the device´s estimation of heart function correlates well with peoples' degree of impairment in activity caused by cardiac dysfunction, except for NYHA class II.
In the Heart function class 1 by Combyn™ ECG 80% (n=80) of individuals reported no, 19% (n=19) slight and 1% (n=1) marked limitation of physical activity.
Of the study participants assigned to NYHA class I 20% (n=80) were estimated to have a Heart function class 1, 47.5% (n=190) a Heart function class 2, 22.8% (n=91) a Heart function class 3 and 9.8% (n=39) a Heart function class 4 by Combyn™ ECG.
In contrast, only 5.5% (n=10) of people with Heart function class 4 complained of symptoms compatible with NYHA class IV. In this Heart function group 35% (n=64) study participants described marked (NYHA III), 38.3% (n=70) slight (NYHA II) and 21.3% (n=39) no decrease in exercise tolerance (NYHA I). The NYHA IV group consisted of 100% (n=10) individuals with an estimated Heart function class 4.
Additionally, 47.7% (n=91) persons with stage 3 Heart function by Combyn™ ECG disclosed no, 35.9% (n=69) only mild and 16.7% (n=32) significant limitation of physical activity.

These results reveal how badly most patients underestimate their degree of functional impairment by cardiac dysfunction and that using the NYHA classification for the assessment of HF severity displays a noticeably low diagnostic accuracy.

4.3 NT-proBNP and NYHA classification

The comparison of the patients' severity of symptoms with serum NT-proBNP levels showed a significant association between the same classes.

In the NYHA I group 46% (n=184) of people had NT-proBNP levels ≤125 pg/ml, 37.3% (n=149) between 125 - 400 pg/ml, 10.8% (n=43) between 401 - 1000 pg/ml and 6% (n=24) levels >1000 pg/ml. Conversely in the NT-proBNP class 1 85.2% (n=184) disclosed no, 12% (n=26) mild and 2.8% (n=6) moderate limitation in physical activity.

All patients (n=10) in the NYHA IV group had NT-proBNP levels above 1000 pg/ml, whereas surprisingly people with these marked elevations in natriuretic peptides clearly underestimated their degree of exercise intolerance caused by HF: 15.8% (n=24) displayed no, 32.9 (n=50) only mild, 44.7 (n=68) moderate and only 6.6% (n=10) severe limitation of physical activity.

Of the 134 individuals with NT-proBNP levels between 401 – 1000 pg/ml 32.1% (n=43), 50% (n=67), 17.9% (n=24) and 0% (n=0) reported symptoms compatible with NYHA classes I – IV.

Pairwise comparisons of the NYHA classification groups were performed and the Kruskal-Wallis revealed significant differences, except for the comparison of class III with class IV. Interestingly ROC curves of NT-proBNP displayed AUCs of 0.81, 0.65, 0.82 and 0.94 respectively for NYHA classes I – IV, revealing a high accuracy for the classes 1, 3 and 4.

The comparison of the patients' severity of symptoms with serum NT-proBNP levels revealed similar results to the comparison with Heart function by Combyn™ ECG, further supporting earlier findings. These data underline the fact that the NYHA classification should only cautiously be used to evaluate and grade symptoms in patients with HF and can eventually result in underestimation and underdiagnosis of HF.

Since almost a century the NYHA classification has been used as a cornerstone for risk stratification and evaluation of symptom severity in HF, enrollment in clinical trials and therapeutic decision making.[14] Despite its ubiquitous application growing evidence has emerged that LV dysfunction correlates poorly to symptom severity in heart disease.[10,14] Although there is a relationship between the degree of limitation in physical activity and higher rates of hospitality and death, morbidity and mortality is still high among patients with lower NYHA classes.[10] The NYHA classification has been shown to perform well in individuals with advanced heart disease (NYHA III/IV), but less so in asymptomatic/mildly symptomatic stages (NYHA I/II).[40]

In their article *“Clinical implications of the New York Heart Association Classification”* Caraballo et. al analyzed 4 landmark HF trials to assess implications of the NYHA classification.[14] They concluded that it poorly discriminates the degree of functional impairment and only insufficiently predicts adverse outcomes in patients with HF.[14] Therefore it´s thoughtless sole use in daily medicine, clinical trials and decision making could impede with the goal to provide optimal medical care for individuals with HF.[14]

A systematic review between NYHA classification and 6-minute walk distance (6MWD) demonstrated well the subjectivity of the NYHA classification, when comparing it with the 6MWD, a more objective test.[40] Concordance among physicians regarding NYHA class evaluation has been shown to be nearly the same as flipping a coin (only 54-56%) and self-reported walking distance by patients hardly ever displays real exercise tolerance.[40] Therefore more objective tests for the assessment of functional status should also be considered.[40]

The 6MWD is a simple and reliable test, that has been shown to have good prognostic implications and independently predict adverse outcomes in patients with HF.[40] Individuals are asked to ambulate on a flat level for 6 minutes and the distance walked is used as a simple and objective assessment of cardiac function and prognosis in HF.[40] Despite its limitations (influenced by non-cardiopulmonary factors, e.g. height and weight and lacking information about the mechanism of exercise limitation) the 6MWD should therefore routinely be included in a thorough cardiovascular examination.[40]

Another easily performed yet objective assessment tool for the evaluation of exercise capacity in subjects with HF is the two-minute step test (2MST).[41] During the 2MST individuals imitate climbing the stairs by marching in place with high knee lifts and the number of knee raises above a certain height is counted within two minutes.[41] After performance patients report a higher level of general fatigue, leg fatigue and dyspnea in comparison to the 6MWD.[41] Especially in individuals with only mild HF ambulating on a flat surface does not elicit a sufficient fatiguing effect.[41] In individuals, who perform the 6MWD without significant efforts, the 2MST may therefore better display limitations of cardiac functional reserve.[41] It can also be used in patients with more advanced HF and additionally offers important information about lower limb muscle endurance.[41]

NT-proBNP levels have a positive correlation with NYHA functional classes, systolic LV internal dimension, systolic and diastolic pressures and correlate negatively with the LVEF.[42] To differentiate dyspnea arising from a diseased heart or a different cause Bozkurt et al. in the HF consensus statement and Song et al. determined a NT-proBNP cut-off level >300 pg/ml.[7,42]
Song et al. found in their study of 348 patients the following mean NT-proBNP levels: 87.9±7.59 pg/mL (n=217) in NYHA class I, 992.8±98.58 pg/mL (n=53) in NYHA class II, 2937.9±451.49 pg/mL (n=50) in NYHA class III and 12127.8±2291.95 pg/mL (n=28) in NYHA class IV.[42]
Our study included 741 individuals with the following results. In the NYHA functional classification group I the mean NT-proBNP levels were 286±470.4 pg/mL (n=400), in group II 1036.7±3096.1 (n=222), in group III 2190.1±5424.3 pg/mL (n=109) and in group IV 5318.5±4765.8 pg/mL.
These data underline the broad variation among levels of natriuretic peptides in the various NYHA stages and further strengthen the argument for the urgent implementation of objective testing into the armamentarium of HF diagnostics.

In conclusion, it should be emphasized that the NYHA classification remains an easily-applicable first-line tool for HF-assessment, but physicians should always keep its subjectivity and potential unreliability in the back of their minds.
Due to its miserable operating characteristics and underestimation of the degree of HF resulting in delayed diagnosis and consecutive poorer patient outcomes it should never be used solely, but always in conjunction with more objective tests e.g. natriuretic peptides, 6MVD, 2MST, etc. These functional tests are easily applicable, objective and provide quick information about the true exercise tolerance of HF patients.

4.4 Heart function by Combyn™ ECG and ECF/ICF ratio in lower extremities

Detection of overhydration by measuring the ECF and ICF by segmental impedance in patients with HF has been shown to be most sensitive in areas exposed to the highest hydrostatic pressure.[43]

Comparison of the ratio of ECF/ICF mean in both lower extremities demonstrated a significant increase in progressive cardiac dysfunction displayed by higher Heart function by Combyn™ ECG classes. Additionally, significant differences between the individual groups were discovered, when analyzing pairwise comparison.

The Kruskal-Wallis test revealed that the Combyn™ ECG distinguishes people with Heart function class 1 well from patients with higher classes (strong effect sizes). Comparison of class 2 with 4 and class 3 with 4 yielded moderately and comparison of class 2 with 3 weakly significant differences. Satisfactory sensitivity and specificity were reached for Heart function class 1 and 4 with AUCs of 0.87 and 0.80, in comparison to 0.6 and 0.67 for Heart function class 2 and 3, respectively.

Therefore, it can be concluded that the Combyn™ ECG performs well at differentiating between people with physiologic and increased extracellular volume status in the lower extremities. The degree of ECF accumulation is significantly correlated with the estimation of the cardiac dysfunction by the Combyn™ ECG.

4.5 Heart function by Combyn^{TM} ECG and amplitude of blood acceleration over the thorax and left leg

A hallmark of advanced heart disease is the progressive decrease in blood acceleration over the aorta caused by overstretching of cardiac myocytes.[6] Increased left ventricular dilatation leads to a reduction of interaction sites between actin and myosin in the heart muscle fibers resulting in weaker myocardial contraction.[6] Through the additional neck electrode we were able to perform impedance measurements to evaluate exactly this aspect of cardiac dysfunction.

Analysis of amplitude of blood acceleration over the thorax revealed significant differences in the Heart function groups, except for the pairwise comparison of class 1 with 2 and class 3 with 4. All other comparisons yielded high effect sizes. The Combyn^{TM} ECG therefore allows the distinction between no to mild from moderate to severe cardiac dysfunction by measurement of blood acceleration over the thorax. AUCs for Heart function classes 1 to 4 were 0.64, 0.68, 0.82 and 0.82 respectively, displayed better sensitivity and specificity in advanced cardiac disease.

Analysis of amplitude of blood acceleration over the left leg also displayed a significant decrease with increasing Heart function by Combyn^{TM} ECG class with moderate to weak effect sizes for all pairwise comparisons. The AUCs were 0.64 and 0.55 for Heart function classes 1 and 2 and 0.64 and 0.74 for Heart function classes 3 and 4, respectively.
ROC-curves of amplitude of blood acceleration in the left leg revealed expectedly lower values than in the thorax, due to the anatomic proximity to the heart of the latter.

5 Conclusion

Using the ECG for diagnosing and classifying HF remains a serious challenge, despite the rapid technical progress in all fields of health care.

The Combyn^{TM} ECG represents a fairly accurate and novel diagnostic tool to not only detect HF and its sequelae during a routine 12-channel ECG, but also provide information about the degree of cardiac dysfunction.

Especially in individuals with low or very high NT-proBNP levels the device performs well appropriately estimating the degree of HF.

Our study shows that many patients with cardiac dysfunction markedly underestimate their true degree of functional impairment. We observed a broad range of NT-proBNP values among all NYHA functional classes and therefore advise clinicians to remain critical about it reliably reflecting the individuals´ true exercise tolerance. The NYHA classification should always be interpreted with caution and in patients with high pretest probability for HF, prompt further testing (e.g. 6MWD, 2MST, NT-proBNP-levels and echocardiography).

Additionally, the Combyn^{TM} ECG enables cardiovascular phenotyping by measurement of amplitudes of blood accelerations over the thorax and legs, in conjunction to beat-to-beat segmental volume changes in the extremities, which have been shown to correlate with the degree of HF.

Its widespread implementation into the diagnostic armamentarium of heart and vascular disease would offer immediate and accurate functional phenotyping and therefore markedly improve diagnostic yield in cardiovascular and metabolic medicine.

6 References

1. Ziaeian, B. & Fonarow, G. C. Epidemiology and aetiology of heart failure. *Nat. Rev. Cardiol.* **13**, 368–378 (2016).
2. Ho, K. K., Pinsky, J. L., Kannel, W. B. & Levy, D. The epidemiology of heart failure: the Framingham Study. *J. Am. Coll. Cardiol.* **22**, 6A-13A (1993).
3. McMurray, J. J. & Stewart, S. Epidemiology, aetiology, and prognosis of heart failure. *Heart Br. Card. Soc.* **83**, 596–602 (2000).
4. Jahmunah, V. *et al.* Computer-aided diagnosis of congestive heart failure using ECG signals - A review. *Phys. Medica PM Int. J. Devoted Appl. Phys. Med. Biol. Off. J. Ital. Assoc. Biomed. Phys. AIFB* **62**, 95–104 (2019).
5. Gaggin, H. K. & Januzzi, J. L. Biomarkers and diagnostics in heart failure. *Biochim. Biophys. Acta* **1832**, 2442–2450 (2013).
6. Skrabal, F., Pichler, G. P., Gratze, G. & Holler, A. Adding 'hemodynamic and fluid leads' to the ECG. Part I: the electrical estimation of BNP, chronic heart failure (CHF) and extracellular fluid (ECF) accumulation. *Med. Eng. Phys.* **36**, 896–904; discussion 896 (2014).
7. B, B. *et al.* Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J. Card. Fail.* (2021) doi:10.1016/j.cardfail.2021.01.022.
8. Yancy, C. W. *et al.* 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.* **62**, e147-239 (2013).
9. Kosaraju, A., Goyal, A., Grigorova, Y. & Makaryus, A. N. Left Ventricular Ejection Fraction. in *StatPearls* (StatPearls Publishing, 2021).
10. Ponikowski, P. *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* **37**, 2129–2200 (2016).
11. Ta, M. *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **42**, (2021).
12. Aa, A., S, M. & M, C. Heart Failure with Mid-Range Ejection Fraction - a New Category of Heart Failure or Still a Gray Zone. *Maedica* **11**, (2016).
13. C, N., Dm, K., Tj, P. & K, D. Beyond pharmacological treatment: an insight into therapies that target specific aspects of heart failure pathophysiology. *Lancet Lond. Engl.* **393**, (2019).
14. C, C. *et al.* Clinical Implications of the New York Heart Association Classification. *J. Am. Heart Assoc.* **8**, (2019).
15. Jj, M. Clinical practice. Systolic heart failure. *N. Engl. J. Med.* **362**, (2010).
16. Jr, K. *et al.* Precipitating Clinical Factors, Heart Failure Characterization, and Outcomes in Patients Hospitalized With Heart Failure With Reduced, Borderline, and Preserved Ejection Fraction. *JACC Heart Fail.* **4**, (2016).
17. Lt, C. Myocarditis. *N. Engl. J. Med.* **360**, (2009).
18. A, M.-N., Pn, H. & M, F. Cardiac amyloidosis. *Clin. Med. Lond. Engl.* **18**, (2018).

19. A, P. Hereditary hemochromatosis. *Biochim. Biophys. Acta* **1763**, (2006).
20. B, B. & K, S. Lysosomal Glycosphingolipid Storage Diseases. *Annu. Rev. Biochem.* **88**, (2019).
21. Y, L., Mh, Z., W, H., J, Z. & Y, L. Wet beriberi with multiple organ failure remarkably reversed by thiamine administration: A case report and literature review. *Medicine (Baltimore)* **97**, (2018).
22. L, F., M, H. & S, C. Primary carnitine deficiency and cardiomyopathy. *Korean Circ. J.* **43**, (2013).
23. J, C. An original discovery: selenium deficiency and Keshan disease (an endemic heart disease). *Asia Pac. J. Clin. Nutr.* **21**, (2012).
24. Ja, T. Inherited cardiomyopathies. *Circ. J. Off. J. Jpn. Circ. Soc.* **78**, (2014).
25. Bj, M. & Ms, M. Hypertrophic cardiomyopathy. *Lancet Lond. Engl.* **381**, (2013).
26. B, I. & A, V. Epidemiology of valvular heart disease in the adult. *Nat. Rev. Cardiol.* **8**, (2011).
27. Td, W. & Jk, O. Constrictive Pericarditis. *Cardiol. Clin.* **35**, (2017).
28. Ao, M., Jr, S., P, C.-S. & M, Y. Endomyocardial Fibrosis: an Update After 70 Years. *Curr. Cardiol. Rep.* **21**, (2019).
29. Ynv, R., V, M., Mm, R., Ra, N. & Ba, B. High-Output Heart Failure: A 15-Year Experience. *J. Am. Coll. Cardiol.* **68**, (2016).
30. Pschyrembel Online | Herzinsuffizienz (HI). https://www-1pschyrembel-1de-10013b4ni0a48.han.medunigraz.at/Herzinsuffizienz%20(HI)/L08PA/doc/.
31. T, K., H, D. & Kc, W. [Pathophysiology of heart failure]. *Internist* **48**, (2007).
32. Mk, A., Ce, A. & B, P. The renin-angiotensin-aldosterone system and its suppression. *J. Vet. Intern. Med.* **33**, (2019).
33. C, H. Essential biochemistry and physiology of (NT-pro)BNP. *Eur. J. Heart Fail.* **6**, (2004).
34. C, H. NT-ProBNP: the mechanism behind the marker. *J. Card. Fail.* **11**, (2005).
35. M, J. Neprilysin inhibition--a novel therapy for heart failure. *N. Engl. J. Med.* **371**, (2014).
36. Kc, S., Pa, N., Zi, A. & Pa, F. Artificial intelligence-enhanced electrocardiography in cardiovascular disease management. *Nat. Rev. Cardiol.* **18**, (2021).
37. M, K., J, K. & B, C. Diagnosis and evaluation of heart failure. *Am. Fam. Physician* **85**, (2012).
38. Rr, van de L. *et al.* Discovering and Visualizing Disease-Specific Electrocardiogram Features Using Deep Learning: Proof-of-Concept in Phospholamban Gene Mutation Carriers. *Circ. Arrhythm. Electrophysiol.* **14**, (2021).
39. Kc, J. *et al.* Blood Pressure Measurement in SPRINT (Systolic Blood Pressure Intervention Trial). *Hypertens. Dallas Tex 1979* **71**, (2018).
40. J, Y. *et al.* Correlation of the New York Heart Association Classification and the 6-Minute Walk Distance: A Systematic Review. *Clin. Cardiol.* **38**, (2015).
41. Węgrzynowska-Teodorczyk, K. *et al.* Could the two-minute step test be an alternative to the six-minute walk test for patients with systolic heart failure? *Eur. J. Prev. Cardiol.* **23**, 1307–1313 (2016).
42. Song, B. G. *et al.* Correlation Between Levels of N-terminal Pro-B-Type Natriuretic Peptide and Degrees of Heart Failure. *Korean J. Intern. Med.* **20**, 26 (2005).

43. F, S. *et al.* The Combyn^{TM} ECG: Adding haemodynamic and fluid leads for the ECG. Part II: Prediction of total body water (TBW), extracellular fluid (ECF), ECF overload, fat mass (FM) and 'dry' appendicular muscle mass (AppMM). *Med. Eng. Phys.* **44**, (2017).