## Diploma Thesis

# Comparison of office heart rate and mean 24-hours ambulatory heart rate in chronic heart failure patients in relation to their ejection fraction

submitted by

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**Doktorin der gesamten Heilkunde**

**(Dr. med. univ.)**

at the

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Graz, 30.03.2020

## *Statutory Declaration*

*I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. The acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the "Guidelines of the Medical University of Graz on Good Scientific Practice".*

*Graz, 30.03.2020* *Vera Habenicht eh*

# Acknowledgement

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I would like to thank all study participants for giving us their time and patience, as no study would be able to be completed without that.

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# Abstract

***Background:*** Chronic heart failure poses a global disease with a prevalence of up to 2%. It comes with a high mortality rate, and is bound to a great financial burden, including extensive treatment costs.

The pharmacological treatment of heart failure aims to improve the ejection fraction and lower the heart rate. The correlation between those two main targets is the main object of this work.

***Methods:*** Patients with chronic heart failure and a reduced ejection fraction of <50% were included in this ambulatory study. The central aim of this study was an evaluation of patient history, an assessment of systolic and diastolic dysfunction of the right and left ventricle, a 24-h ambulatory blood pressure and heart rate measurement and an office heart rate measurement. Blood samples were taken and laboratory parameters, such as NT-proBNP, were closely examined.

***Results:*** 99 patients, 20 female and 79 males, with a mean age of 64.8±9.6 years were included in the study. The mean left ventricular ejection fraction was 35.1±9% in the biplane and 34.1±9.3% in the 3D measurement. Median NT-proBNP was 1301.5 pg/mL (IQR: 346.51-2775.3pg/mL). The mean ambulatory heart rate measurements in the main study group were 68.3±10.9 bpm for the overall measurement, during the day 68.3±10.9 bpm and 63.9±10.7 bpm during the night. The mean office heart rate in sitting position was 68.5±13.3 bpm and 71.9±15.9 bpm in supine position (during 12-lead ECG measurement).

***Conclusion:***

The study has shown no significant correlations between different heart rate measurements and left ventricular ejection fraction. Mean ambulatory heart rate measurements strongly correlated with each other, as well as with the mean sitting office heart rate measurement. A single heart rate measurement during ECG did not correlate with the ambulatory heart rate measurements or the mean sitting office heart rate measurement. The significance of this finding remains unclear, and should be further investigated.

# Zusammenfassung

***Hintergrund:*** Die chronische Herzinsuffizienz stellt eine globale Erkrankung mit einer Prävalenz von ca. 2% dar. Sie ist mit einer hohen Mortalität, wie auch hohen finanziellen Ausgaben verbunden. Die medikamentöse Therapie der Herzinsuffizienz zielt primär auf eine Verbesserung der Auswurfleistung und Senkung der Herzfrequenz ab. In dieser Arbeit werden die Korrelation bzw. fehlende Korrelation dieser Parameter als zentrales Thema behandelt

***Methoden:*** Es wurden 99 ambulante PatientInnen mit chronischer Herzinsuffizienz und linksventrikulären Auswurfleistung (LVEF) von <50% eingeschlossen. Das Ziel dieser Studie war eine detaillierte Evaluation der PatientInnengeschichte, eine transthorakale, echokardiographische Untersuchung der systolischen und diastolischen Dysfunktion, die Messung des ambulanten Blutdrucks und der Herzfrequenz, sowie eine Herzfrequenzmessung im Rahmen der Untersuchung in sitzender (multiple Messungen), sowie liegender Position (einmalige Herzfrequenzmessung während eines 12-Kanal EKGs). Außerdem wurde eine Blutabnahme wurde getätigt, und besonderes Augenmerk auf den Herzinsuffizienz-Parameter, dem NT-proBNP -Wert gelegt.

***Ergebnisse:*** 99 PatientInnen, davon 20 weiblich, mit einem mittleren Alter von 64.8±9.6 konnten in den Ergebnissen berücksichtigt werden. Die mittlere Auswurfleistung was 35.1±9% in der biplanaren und 34.1±9.3% in der 3D Messung.

Der mediane NT-proBNP Wert war 1301.5 pg/mL (IQR: 346.51-2775.3pg/mL). Die durchschnittliche Herzfrequenz in der ambulanten Messung war 68.3±10.9/min, während der Tagesmessungen 68.3±10.9/min und während der nächtlichen Messungen 63.9±10.7/min. Die mittlere Messung in sitzender Position während des Untersuchungsaufenthalts war 68.5±13.3/min und 71.9±15.9/min während des 12-Kanal EKGs. Eine Korrelation zu der Herzfrequenz während des EKGs zeigte sich nicht. Ebenso konnte keine Korrelation zwischen der Herzfrequenz und der LVEF gezeigt werden.

***Fazit:***

Es konnte keine Korrelation zwischen den verschiedenen Herzfrequenzmessungen und der Auswurfleistung nachgewiesen werden.

Die mittleren, ambulanten Herzfrequenzmessungen korrelierten sowohl untereinander als auch mit der mittleren Herzfrequenz während des Sitzens, jedoch konnte keine Korrelation der oben genannten Herzfrequenzmessungen zu der Herzfrequenzmessung des EKGs

dargestellt werden. Die Signifikanz dieses Ergebnisses ist unklar und sollte in weiteren Studien beleuchtet werden.

# Abbreviations and definitions

| | |
|---|---|
| (m)24hdayHR | mean 24-hour day heart rate |
| (m)24hnocHR | mean 24-hour nocturnal heart rate |
| ABPM | ambulatory blood pressure monitoring |
| AC | adenylyl cyclase |
| ACE | angiotensine converting enzyme |
| ACh | acetylcholine |
| ACS | acute coronary syndrome |
| AF | atrial fibrillation |
| ARNI | angiotensin receptor-neprilysin inhibitor |
| AV | atrioventricular |
| BMI | body mass index |
| BNP | brain natriuretic peptide |
| BP | blood pressure |
| bpm | beats per minute |
| BSA | body surface area |
| $Ca^+$ | calcium ion |
| cAMP | cyclic adenosine monophosphate |
| CMR | cardiac magnetic resonance |
| CO | cardiac output |
| CRT | cardiac resynchronization therapy |
| ECG | echocardiogram |
| EDTA | ethylenediaminetetraacetic acid |
| EF | ejection fraction |
| ESC | European Society of Cardiology |
| GFR | glomerular filtration rate |

| | |
|---|---|
| HF | heart failure |
| HFmrEF | heart failure with mid-range ejection fraction |
| HFpEF | heart failure with preserved ejection fraction |
| HFrEF | heart failure with reduced ejection fraction |
| H-ISDN | hydralazine–isosorbide dinitrate |
| HR | heart rate |
| INNs | international nonproprietary names |
| $K^+$ | potassium ion |
| LVEF | left ventricular ejection fraction |
| LVVed | end-diastolic left ventricular ejection fraction |
| LVVes | end-systolic left ventricular ejection fraction |
| m24hHR | mean 24-hour heart rate |
| MR antagonist | mineralocorticoid receptor antagonist |
| N | number |
| $Na^+$ | sodium ion |
| NHYA | New York Heart Association |
| NTproBNP | N-terminales pro brain natriuretic peptide |
| OAC | oral anticoagulants |
| SA-node | sinoatrial node |
| Scr | serum creatinine |
| SR | sinus rhythm |
| SV | stroke volume |
| TIA | transient ischemic attack |

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# 1 Introduction

## 1.1 Scope of the problem

Heart failure (HF) is a global problem, concerning over 6.5 million people in the United States alone. Its prevalence is estimated to be over 37.7 million people worldwide and although there is quite a discrepancy in the literature about the exact number, one thing is made clear: heart failure concerns everyone and is still an increasing problem. (1,2)

Its 5- year mortality rate is also similar to many cancer mortality rates, and comes with a great financial burden, costing up to US$20.9 billion in 2012 annually and is estimated to be up to $53.1 billion by 2030. (3)

In Germany, heart failure is the most common cause for disease-related hospitalization and also accounts for the highest in-hospital mortality in Germany. (4)

## 1.2 Chronic heart failure

### 1.2.1 Definition

According to its definition, heart failure (HF) is a clinical syndrome, where typical symptoms must be present to be defined as such. These symptoms include dyspnoea, ankle swelling and fatigue, whereas dyspnoea on exertion was found to be the most specific. Before clinical symptoms are evident, patients may present with asymptomatic left ventricular systolic dysfunction. (5,6)

HF is not only characterized by a decline of cardiac output but also by a change of neuro-hormonal mechanisms, including the activation of the sympathetic nervous system as well as activating cytokines and the renin-angiotensin-aldosterone-system. This neuro-hormonal activation then leads to the clinical image of tachycardia. (7)

### 1.2.2 Terminology

HF can be subdivided into different groups, depending on the severity, the duration of HF and the left ventricular ejection fraction (LVEF).

The terminology, which relates to the time course of heart failure, grades the syndrome according to the New York Heart Association (NYHA) classification. Patients, who experience signs and symptoms of heart failure over an extended period of time are classified to have chronic HF. Acute HF may present as a consequence of an acute myocardial infarction or a myocarditis and may resolve over time.

The main terminology which is used is based on the measurement of the LVEF and can roughly be divided into two groups: patients with preserved LVEF (>50%) and patients with reduced LVEF (<40%). The epidemiology those two group are found two differ completely and are only linked by a group of patients with a LVEF between 40-49%, who are believed to have epidemiology that cannot clearly be placed in either one of those groups. (6)

All the patients included in this study presented with chronic HFrEF.

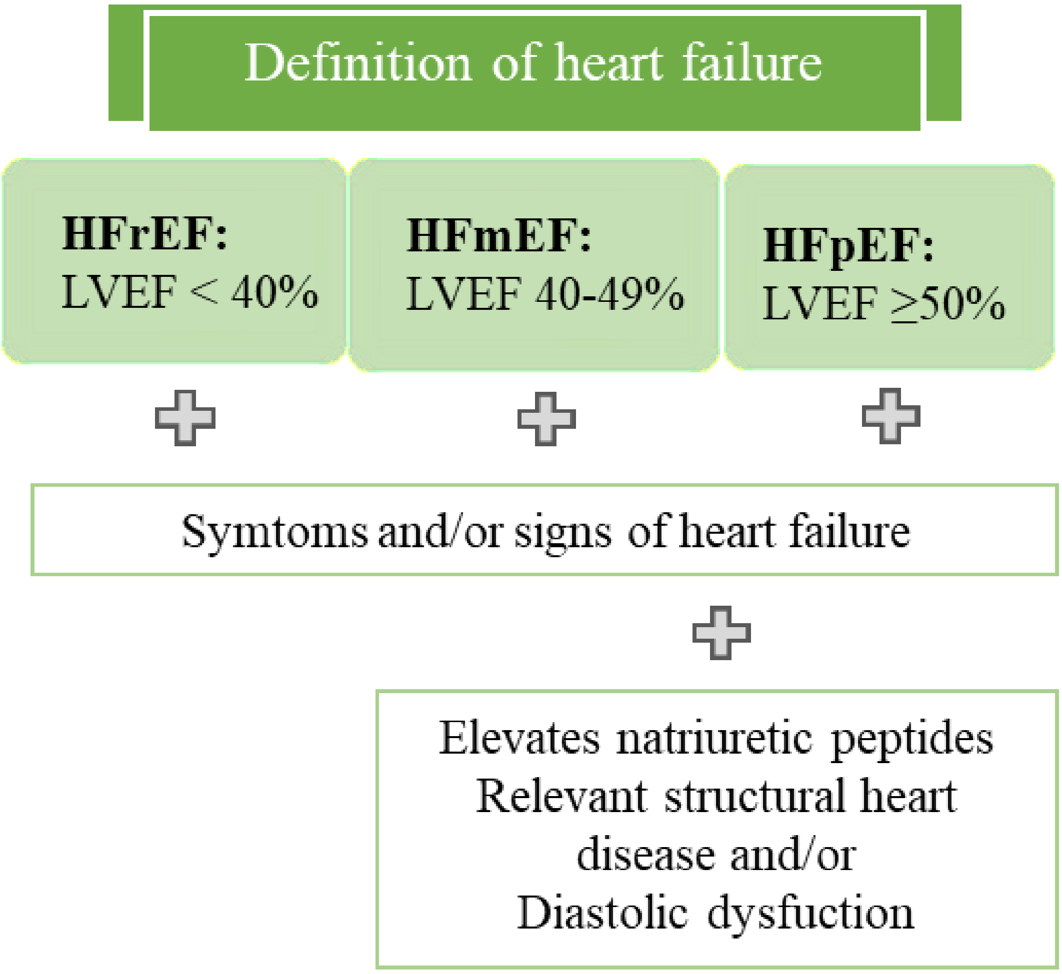


**Figure 1:** Definition of the different forms of heart failure
HFrEF= heart failure with reduced ejection fraction
HFmEF= heart failure with mid-range ejection fraction
HFpEF= heart failure with preserved ejection fraction
LVEF=left ventricular ejection fraction

### 1.2.3 Epidemiology and aetiology

The population of patients with HFrEF is younger and man-dominated compared to HFpEF patients. There is no clear classification system for HF, as the aetiology is so diverse. Most of the time patients present with multiple pathologies, cardiovascular and non-cardiovascular, that add up to the clinical syndrome of heart failure. Cardiovascular pathologies range from diseased myocardium, such as ischemic heart disease, toxic damage and genetic abnormalities, to abnormal loading conditions. As all those pathologies can be subdivided further, it makes it obvious that diagnosing heart failure can be tricky. (6)

### 1.2.4 Diagnosis

Firstly, the diagnosis of HF must include a well performed physical examination and a detailed assessment of the patient’s medical history. HF is unlikely in patients without relevant medical history but probable in patient with previous cardiac events such as acute myocardial infarction. Typical signs that can be seen during physical examination include elevated jugular pressure, heart murmur and a displaced apex. The combination of dyspnoea, apex displacement and history of myocardial infarction makes the diagnosis almost unquestionable. Secondly, natriuretic peptides have been proven to be a good initial diagnostic marker and should be evaluated. If NT-proBNP is within the normal range (125 pg/mL), HF is unlikely. It should not solely be used to establish the diagnosis of HF, as it can be elevated to various other causes. In order to assess the disease progression, signs and symptoms must be revaluated at each consultation. The golden standard of HF diagnosis is the echocardiography and should be performed if HF is probable after evaluating the steps mentioned above.(5,6)

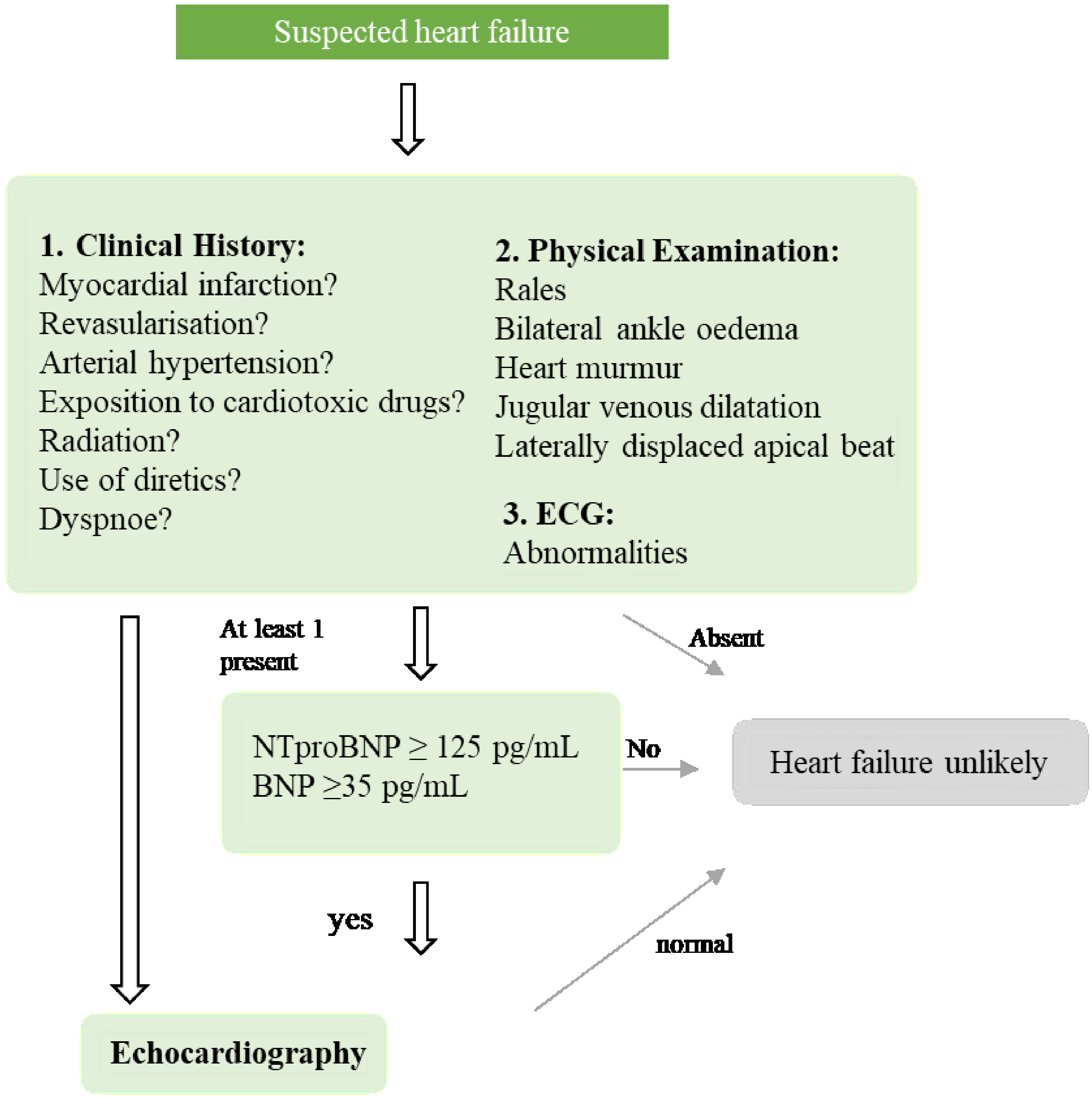


**Figure 2** Suggested procedure for suspected heart failure
ECG: echocardiogram
NTproBNP: N-terminal pro brain natriuretic peptide
BNP: brain natriuretic peptide

### 1.2.4.1 Echocardiography

An echocardiography is an obligatory tool when diagnosing HF was found to be the best choice for assessing the heart's systolic and diastolic function of both ventricles. It bears no concerns about radiation and can be used directly at the patient's bed. The downside to this particular exam is that it is highly dependable on the user and the device, as the fluctuation range is quite large.

The exam is routinely performed transthoracically and can be further subdivided into two- and three-dimensional measurements, the latter with better accuracy of LVEF measurements when being in good quality.

According to ESC guidelines, the left ventricular ejection fractions should be determined by using the modified biplane Simpson's rule, as other methods of measurements, such as Teichholz and Quinones, have shown to being prone to inaccuracies.

The modified Simpson method relies on tracing the end-diastolic and end-systolic endocardial border. The cavity of the left heart chamber is then subdivided into a specific number of discs, eventually leading to the longitudinal contraction of the left ventricle.

Under standard settings a transthoracic echocardiography is enough to determine and classify HF, however in some clinical settings a transesophageal echocardiography is required. It is performed when the severity of valve disease is incongruent with the patients' symptoms, when an endocarditis is suspected, in congenital HF as well as when patients with AF are in need for a cardioversion. (6,8)

### 1.2.4.2 Cardiac magnetic resonance

The best method to determine the volume, mass and ejection fraction of both the left and the right ventricle is the cardiac magnetic resonance (CMR).

It is used when the results of the echocardiography are inconclusive, especially when imaging the right heart and it is also the method of choice for patients presenting with complex congenital HF.

The CMR can also differentiate between ischaemic and non-ischaemic HF.

However, the usage of CMR relies on local expertise, is bound to greater costs and its availability is yet limited. (6)

#### 1.2.4.3 N-terminal pro-brain natriuretic peptide (NT-proBNP)

In the recent years, the measurement of NT-proBNP gained relevance in both diagnosing and treating HF. Natriuretic peptides have found to be independent predictors for mortality and outcome in patients with chronic HF.

It correlates with age, sex and its elevation is directly proportional to prognosis, NYHA score, intra-ventricular pressure and correlates indirectly with cardiac output.

BNP is primarily secreted by ventricles and is synthesized in the heart as a consequence of cardiac wall distension. Its secretion leads to natriuresis and vasodilation. (9)

The measurement of NT-proBNP has a negative predictive value of 99%, hence being a good test for ruling out HF. Plasma concentrations of NT-proBNP lower than 125 pg/ml makes a presence of HF, acute or chronic, unlikely. If the concentration exceeds that amount, HF is possible, the sensitivity of the test being described to be at 75%, respectively. The rule-in cut-off for HF is largely dependent on the age of the patient, for patients younger than 75, the cut-off 900 pg/ml, for patients older than 75, the cut-off doubles itself to 1800 pg/ml.

Moreover the pharmacological management of HF can be improved by using NT-proBNP as a guiding tool, and medication can be up-titrated accordingly.(10)

## *1.3 Heart Rate physiology*

The heart rate is mainly influenced by the sympathetic and parasympathetic nervous system, both being perpetually active.

Whereas the sympathetic nerves innervate the whole heart, the parasympathetic fibers have a more restricted area. They are only present around the atrioventricular (AV) - and the sinoatrial (SA) node and are scarcely found at the ventricles.

The SA-node is characterized by its slow diastolic repolarization and for initiating a rhythmic contraction. In order for that to happen, an inward current is needed. (11)

During rest, the parasympathetic influence predominates, leading to a resting heart rate of around 60 bpm (This number largely variates between individuals). (12)

Rate regulation is primarily based on changing the duration of the diastolic phase. When the sympathetic influence on the heart is predominant, the slope of cardiac depolarization is steeper, whereas the diastolic phase is prolonged, when the parasympathetic influence is higher. (13)

This makes the diastolic depolarization a very important pharmaceutical target.

### 1.3.1 Sympathetic influence on the heart

Noradrenaline binds to $\beta_1$-adrenoreceptors, which then leads to the opening of sodium and calcium ion channels.

Adrenaline answers to this sympathetic stimulation and also binds to $\beta_1$-adrenoreceptors. Its key features are to fasten the pacemaker depolarization and to increase the slow inward current, consisting of calcium and sodium ions.

These changes in the heart lead to following positive effects (12):

- Chronotropic effect: Heart rate rises
- Dromotropic effect: Increased AV-node conduction velocity
- Inotropic effect: Contractility increases
- Lusitropic effect: Faster relaxation

### 1.3.2 Parasympathetic influence on the heart

The parasympathetic nerve is under the influence of the vagal nerve, cranial nerve X.

The neurotransmitter in this pathway is acetylcholine (ACh), which on his part activates muscarinic $M_2$ – receptors.

ACh has two different ways of working, depending on the concentration present. Low dose ACh has shown to inhibit If-channels, whereas high dose ACh- concentration activates ACh- dependent potassium ion channels, which slows the rate of spontaneous depolarization that consequently leads to an extended repolarization phase.

ACh can be quickly removed by cholinesterase, making it a very fast response system. (12,13)

### 1.3.3 B $_1$-adrenoreceptors

B $_1$-adrenoreceptors solely respond to the sympathetic nervous system.
As soon as $\beta_1$-adrenoreceptors are activated, they themselves trigger a biochemical cascade which amplifies the signal and provokes changes in ion channels.
As it would get too detailed, to describe every single step in this work, one channel was picked out, due to its impact on the treatment of HF.

#### 1.3.3.1 Regulation of heart rate: $I_f$ channels

The If- channels are under the control of the so-called funny current. The following features are responsible for the name given:
Being carried by sodium and potassium ion channels, the current is activated on hyperpolarization. It has an inward current and its voltage range contains the range of diastolic depolarization.
Furthermore, the If- channels are activated at the end of each action potential, hence being responsible for generating of diastolic depolarization.

The If-current is positively influenced by $\beta_1$-adrenoceptors, creating a more positive voltage, thus creating a more inward current, which is leading to a steeper diastolic depolarization slope. This is done by a phosphorylation process and by directly binding to the receptors, which then leads to a positive chronotropic effect.

As the If-current also underlies the parasympathetic influence, the voltage can be changed to a more negative one by the influence of ACh. This, on its behalf, is able to inhibit the production of adenylyl cyclase (AC) and cyclic adenosine monophosphate (cAMP), which leads to the inhibition of the If-current itself, consequently slowing down the heart rate. (11,13,14)

### 1.3.4 Adaption of the heart to physical stress

If the heart is exposed to physical stress, the cardiac output can increase to a fourfold of its normal output, meaning it increases up to 25l/min. For more blood to be circling, both the stroke volume (SV) and the heart rate must adapt. Aside from the Frank-Starling mechanism, the sympathetic influence on the heart increases, which increases both contractility and heart rate. This happens way faster than the Frank-Starling mechanism, therefore making the rise of heart rate the first adaption to physical stress. (15) The contractility is increased due to an enhanced re-uptake of calcium ions into the sarcoplasmic reticulum. This is the result of more sodium ions being brought into the myocardial cells through each wave of depolarization. They can then be ejected by the sodium pump, which consequently leads to a sodium overload, which then leads to an increase of cytosolic calcium. This ability of the heart is called the force-frequency relation. (16) This phenomenon, that when the heart rate rises, so does the contractility, was first described by Dr. H.P. Bowditch in 1871, and is therefore also called The Bowditch Treppe. (17)

When the heart rate is increased, both the systole and the diastole are shortened, which might lead to the false conclusion that the SV must consequently decrease. This does not happen in healthy hearts as most of the ventricular filling happens during the first third of the diastole. The SV only decreases if the heart rate exceeds 200 bpm. (15)

## *1.4 Heart rate in chronic heart failure*

### 1.4.1 Pathophysiology

The equilibrium, of sympathetic and parasympathetic influence on the heart, is no longer intact, as the sympathetic influence is predominant, consequently augmenting the resting heart rate. This prevailing influence is believed to be due to the correct baroreceptor reflex, which is responding to a lower SV and an increased end-diastolic pressure, hence allowing sympathetic activation. When HF advances, ordinarily suppressed autonomic reflexes are recruited, leading to an augmented neural and adrenal catecholamine release. This imbalance of sympathetic and parasympathetic influence has been found to be an independent risk factor for disease progression and is therefore a crucial parameter for diagnosis and prognosis. (18,19). More specifically, the baseline heart rate was found to be an independent risk predictor all-cause mortality, cardiovascular mortality and hospitalization, related to their HF, in HF patients. (20)

The consequences of an elevated heart rate are a decrease of coronary perfusion time, an increase of myocardial oxygen consumption, both leading to a myocardial ischemia. There is also experimental data demonstrating the impact on developing of arteriosclerosis and plaque disruption. (20)

### 1.4.2 Heart rate control

Decreasing the heart rate has two main consequences concerning the myocardium itself. Firstly, the diastolic phase of the cardiac cycle is increased, and the perfusion time of the myocardium itself is longer. Secondly, the myocardial oxygen demand is also reduced, leading to a better relation of oxygen demand and supply, the primary cause for angina pectoris. (19,21) As far as the left ventricle is concerned, the filling time is increased, consequently leading to a higher SV. As the EF is increased, so is the reverse remodelling, marked by a regression of myocardial mass and a normalization of ventricular shape. (22,23)

Furthermore, studies have shown an almost linear relationship between the reduction of the resting heart rate and the mortality rate. (24)

#### 1.4.2.1 Beta-Blockers

Beta blockers play a major role of the baseline therapy and should be given, together with ACE-inhibitors, as soon as the diagnosis of HFrEF is being made. (6,7,23) Due to its affinity to adrenergic receptors, airway-diseases represent a contraindication, together with bradycardia, conduction system disease and sinus node disease as well as haemodynamic decompensation. Once being introduced to beta-blockers, the therapy should be retained indefinitely, as the chance of HF deterioration or drug withdrawal is inevitable. (23)

The general effects of beta blockers are as follows: increase of left ventricular function, enhancement of reverse remodelling, reduction of hospitalization due to HF and mortality, all documented in numerous trials over the years.

These positive effects are time-dependent, meaning that they only occur after a treatment exceeding 3 months and are a biological effect of beta blockers, than a pharmaceutical one. (23)

Patients may experience increased bradycardia and intermittent claudication as side effects. (25) Furthermore, a slightly increased risk of fatigue and sexual dysfunction has also been proven, yet not in any relation to the positive effect of beta blockers in HF. (26)

### 1.4.2.2 Ivabradine

Ivabradine is a highly selective If- channel blocker, which distinguishes it from any other drug, as it solely reduced the heart rate without changing any other hemodynamic parameter.

More precisely speaking, ivabradine binds to the intracellular side of the If- channel. In order for it to reach the inner side of the cell, the channel must be open.

As described in the physiology chapter (Chapter 1.3.3.1), funny channels are voltage dependent and are activated after each action potential. This makes it obvious that heart rate and the number of channels being open, are directly proportional. Therefore, penetrating the cell is easier during higher heart rates and ivabradine is more effective, making it a so-called use-dependent drug. When the heart rate is within the physiological range and the parasympathetic influence predominates, the If- channels are closed, making it very difficult for ivabradine to enter the cell, meaning there is no pharmacological effect of the drug, hence leaving out the side effect of bradycardia. (14,22)

Due to its high selectivity, it might lead to the conclusion that it has no side effects. But in 2-3% of all patients it leads to visual symptoms, as it inhibits a similar-looking current the so-called I(h)- current in the retina. (22)

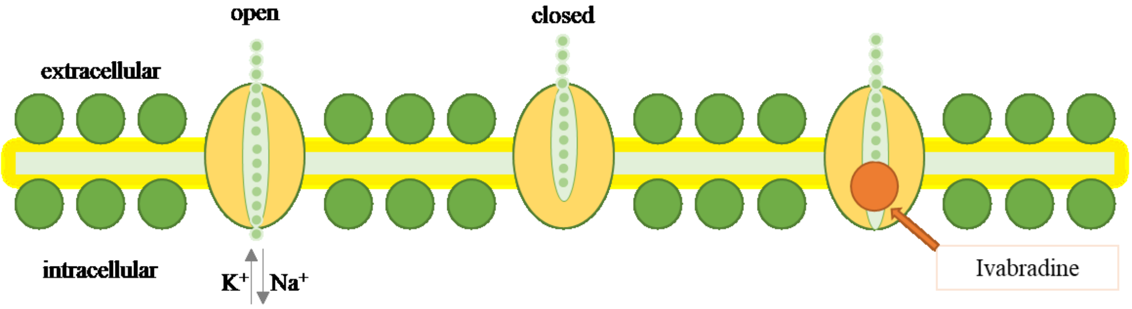


**Figure 3**: A schematic illustration of the working mechanism of ivabradine, needing an open channel to bind to the intracellular part of the cell

In the SHIFT trial (27), a study which was published 2010, over 6000 patient received ivabradine in addition to their guideline-based HF medication. This was a double-blinded, placebo-controlled study, which included patients with a EF <35% and a heart rate > 70 bpm. The aim of the study was to evaluate the cardiovascular outcomes (The primary endpoint being a mixture of being admitted to the hospital due to cardiac decompensation and death due to HF.), symptoms and quality of life in patients with chronic HF.

The relative risk of a primary endpoint fell by 18% in the group of patients who got ivabradine, compared to the placebo treatment. It should be noted, that only in the subgroup of patients with a baseline heart rate of >77 bpm a significant treatment effect was observed.

After one year of treatment, heart rate difference between placebo and ivabradine was 8.1 bpm, being lower in ivabradine patients, as expected (Fig. 2). It was also observed, that patients with a baseline heart rate exceeding the median, had a higher beneficial use of ivabradine, compared to those with a lower heart rate than the median. This suggests that the benefit ivabradine- treatment highly relies on the resting heartrate prior to treatment, thus underlining the importance of precise heart rate evaluation prior to HF treatment.

### 1.4.2.3 Digitalis

For a long time, cardiac glycosides used to be the best treatment option for HF, due to their positive inotropic effect. It was only in 1997, that a huge study (DIG-Study) found no effect on patient's mortality, only a decrease on their rate of hospitalization and an increase of physical fitness. Thereafter glycosides were only used in combination with diuretics and ACE- inhibitors or beta-blockers.

Cardiac glycosides partially inhibit the magnesium dependent Na+/K+-ATPase, hindering sodium ions to exit the cell, whereas potassium ions are not able to get into the cell. As the intracellular Na+ concentration gets higher, another channel is getting involved: The Na+/Ca+ trans-membranous channel, that normally exchanges one intracellular calcium ion with three extracellular sodium ion is now blocked due to the already high intracellular sodium concentration, this consequently increases the intracellular calcium level.

During the diastole more calcium ions are stored in the sarcoplasmic reticulum, and are released during the systolic phase, resulting in an increase of force, hence being positively inotropic.

Due to these abilities, the sympathetic involvement is lowered, and so is the heart frequency, explaining the negative chronotropic effect of cardiac glycosides. As the diastole is prolonged, so is the filling phase, again resulting in an increase of the EF and the cardiac output (CO).

Nowadays cardiac glycosides are used to treat severe HF, atrial flutter and atrial fibrillation (AF), in combination with the HF medication mentioned above. Due to their small therapeutic index, cardiac glycosides should only be given after careful consideration and even then, there is a chance of a vast variety of side effects, including headaches, visual impairments, arrhythmias and drowsiness in about 20% of all patients.

When the therapeutic index is exceeded by a twofold (or sometimes even less), there is a chance of intoxication and all the side effects can occur more intensified, with arrhythmias being the most dangerous, as it can lead to AV-blocks, bradycardias and ventricular fibrillation and ultimately death.

Their contraindications can be derived from their side effects, hence should not be given to bradycardic patients, patients with arrhythmias, or with aortic stenosis, as well as to patients with suspected intoxication with cardiac glycosides. (28)

#### 1.4.2.4 Amiodarone

Amiodarone blocks multiple repolarization and depolarization channels, making it a multi-channel blocker. It decreases Ca+ current, blocks inactivated Na+ channels to decrease conduction velocity and non-competitively blocks adrenergic receptors. These vast blocking abilities lead to frequent prolongations of PR-, QRS- and QT- intervals and sinus bradycardia, when given for an extended period.

Structurally, amiodarone is an analogue to a thyroid hormone and some of its actions and toxicity derives from interacting with nuclear thyroid hormone receptors.

Despite the broad spectrum of adverse effects, which includes photo sensibility, corneal microdeposits, hypo- and hyperthyroidism, nausea and pulmonary fibrosis, amiodarone is widely used to treat AF and common arrhythmias that are not manageable otherwise as well as in the acute setting of ventricular fibrillation and recurrent ventricular tachycardia. They should generally be restricted to a short-term use in patients with paroxysmal or persistent AF.

Furthermore, as amiodarone is lipophilic, it tends to accumulate in different tissues meaning that when the drug is withdrawn from the patient, it takes weeks to months to eliminate all.

Amiodarone is contraindicated in sinus bradycardia, prolonged QT interval, pregnancy and hyperthyroidism. (6,28,29)

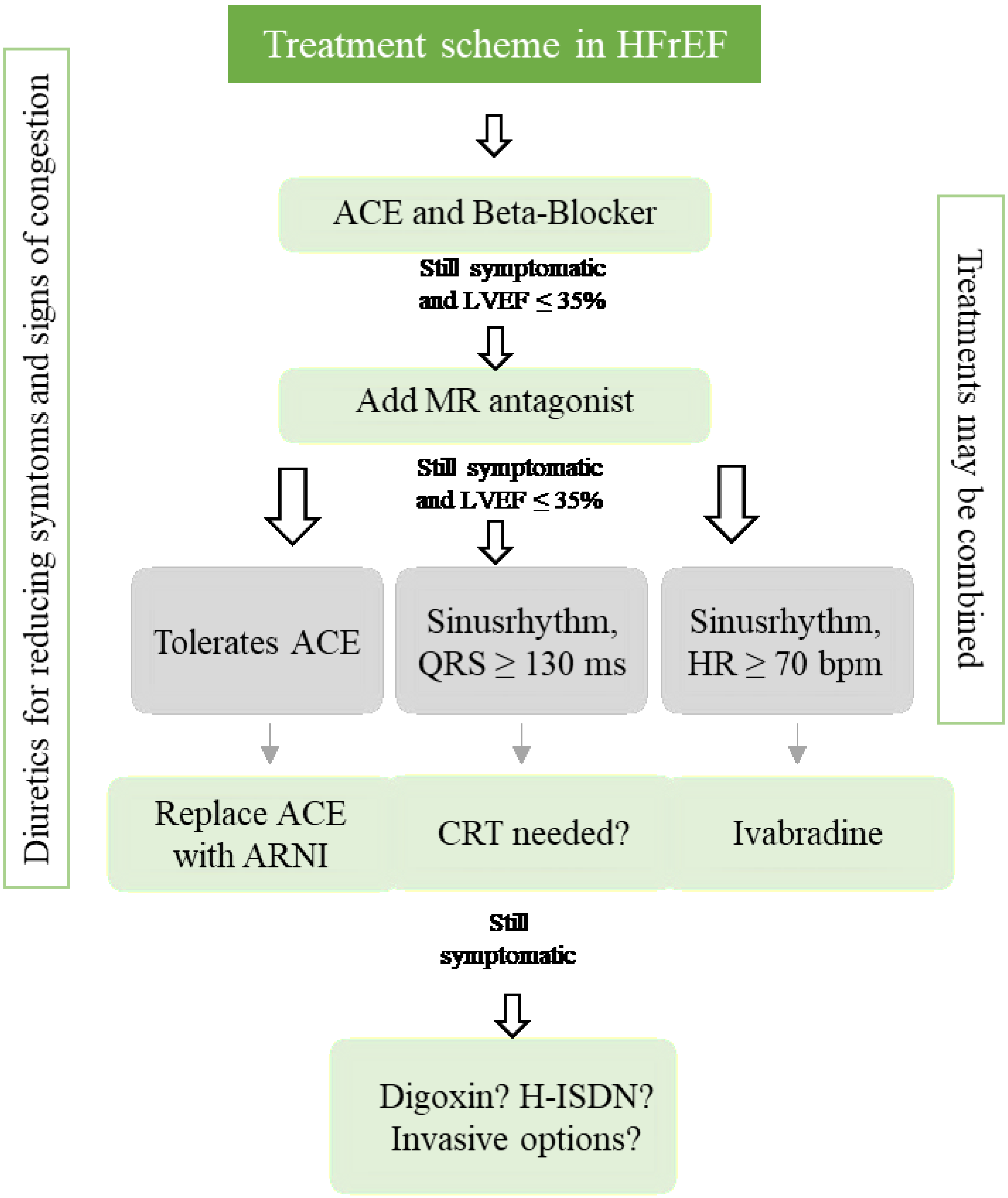


**Figure 4:** ESC guidelines: Therapeutic algorithm for patients with symptomatic HFrEF
ACE: Angiotensine converting enzyme
ARNI: angiotensin receptor-neprilysin inhibitor
CRT: Cardiac resynchronization therapy
H-ISDN: hydralazine–isosorbide dinitrate
MR antagonist: mineralocorticoid receptor antagonist

## 1.5 Atrial fibrillation in heart failure

AF represents the most common arrhythmia for hospitalization and medical treatment. The pathophysiology behind this arrhythmia is manifold and includes atrial stretching, ischemia, sympatho-vagal influences, inflammation and HF. (30)

The prevalence of AF in an adult population is 3%, is increased in HF patients.

They are often linked together and up to 30% of patients with AF present with left ventricular dysfunction. AF and HF can exacerbate each other through structural remodelling, neuro-hormonal changes and rate-related impairment of the left ventricle. A worse outcome and all-cause mortality is predicted in patients who present with both AF and HF. Patients who present with AF prior to HF tend to have a more benign outcome to those who develop AF after being diagnosed with HF, latter is believed to be due to the already present impairment of the left ventricle, hence being a marker of a sicker patient. The chance of developing AF in HF patients can be reduced with the correct HF treatment, including the medication mentioned above, excluding ivabradine, which may increase the chance of development.

Additionally, to normal HF treatment, patients with concomitant AF should be given oral anticoagulants (OAC), as this is the only treatment with proven prognostic value. The rate control should be evaluated through a 12-lead echocardiogram (ECG) and should ideally be assessed during rest, sleep and exercise. The ideal heart rate in HF patients with AF is yet unclear and is currently stated to be between 60- 100 bpm. The overall outcome in patients with a ventricular rate lower than 70 bpm seems to be worse. In case of the failure to reduce the heart rate lower than 110 bpm an AV node ablation and implantation of a ventricular pacing device needs to be considered. (6,31)

## 1.6 *Gaps in evidence*

### 1.6.1 Atrial fibrillation and heart rate control

Lowering the heart rate means having a better prognosis in HF patients, this has been well described by many authors, starting with the Framingham study. But this statement is only true for patients who present themselves in sinus rhythm (SR).

Yet, the prevalence of presenting with AF ranges from 17-27% and may even peak to 50% for patients with severe HF (32,33).

In general, a heart rate between 60-100 bpm is advised for HF patients with AF (6), but there is an evident lack of long term studies, which concern the treatment options and its intensity for managing heart rate in HF patients. (31)

There is no clear statement if (and to what extent) lowering the patient's heart rate should be a target in AF patients with HF as lowering the heart rate only seems to improve the all-cause mortality in patients with SR. (34)

*Cause or consequence?*

When looking further into the HF studies, which cover the topic of patients with AF, most studies do not differentiate whether AF was derived from HF or was present beforehand. It is not clearly stated, whether this knowledge would make a difference in treatment and its success.

### 1.6.2 Heart rate as a snapshot

In order to determine the patient's resting heart rate, a 12-lead ECG should be performed, from which the pharmacological treatment options will be defined. There is no mention of the ambulatory heart rate measurements or repetitive, mean heart rate measurements. (6)

Hence, the follow-up measurements derive from a single measurement again, making it a rather fault-prone parameter.

## 1.7 Hypothesis and aims of the thesis

The correlation of heart rate and ejection fraction has been questioned in this work. It is assumed that the nightly heart rate correlates best with the left ventricular ejection fraction.

# 2 Materials and Methods

## 2.1 Data collection

The RoC-HF study (Role of Comorbidities in Heart Failure, NCT02922478) is a prospective, single-centered cross-section study. Patients' inclusion, which followed the underlying study protocol, was executed after the approval of the ethics commission of the Medical University of Graz.

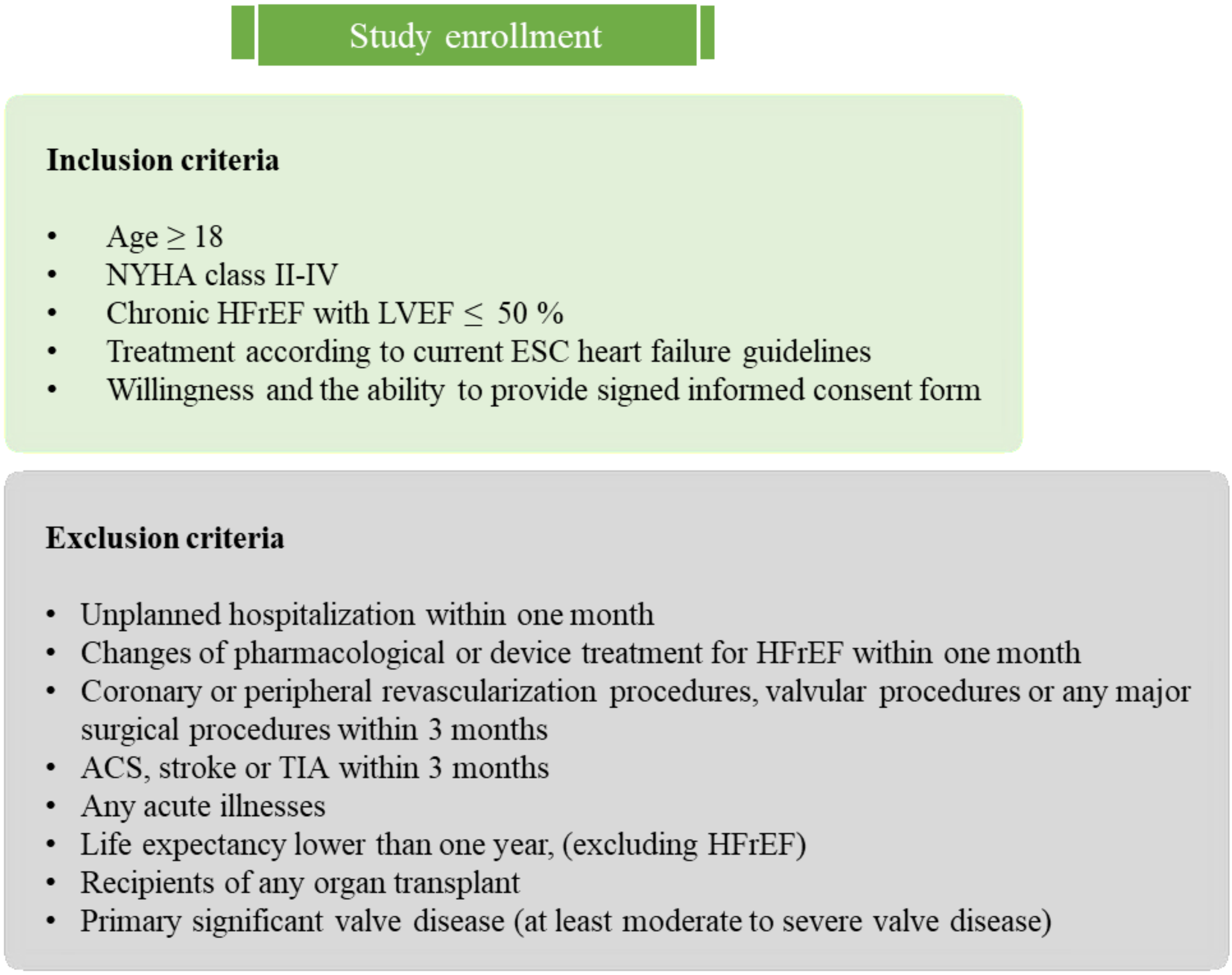
Potential study subjects were selected from HF patients, who routinely visited the department of cardiology of the Medical University of Graz. They were then contacted and thoroughly briefed about the study. All patients have given written informed consent according to the World Medical Association Declaration of Helsinki, 2013.

## 2.2 Demography

The study population consisted of male or female subjects with stable chronic HF with reduced ejection fraction, according to the ESC HF Guidelines of 2016. Each patient was contacted personally through the department of Cardiology or the Department of Internal Medicine in Graz. The data collection in this study includes 99 patients, who were included in the Roc-HF study during the time period of September 2016 to December 2017.

From the demographic data which was collected throughout the study (including age, height, weight, waist and hip circumference, circumference of the non-dominant upper arm and ethnic group) the BMI, the gender and the age was used in this work. The study population consistent solely of Caucasian people, hence no adaption of laboratory parameters (e.g. GFR) needed to be made.

### 2.2.1 Criteria for study enrollment



Study enrollment

**Inclusion criteria**

- Age ≥ 18
- NYHA class II-IV
- Chronic HFrEF with LVEF ≤ 50 %
- Treatment according to current ESC heart failure guidelines
- Willingness and the ability to provide signed informed consent form

**Exclusion criteria**

- Unplanned hospitalization within one month
- Changes of pharmacological or device treatment for HFrEF within one month
- Coronary or peripheral revascularization procedures, valvular procedures or any major surgical procedures within 3 months
- ACS, stroke or TIA within 3 months
- Any acute illnesses
- Life expectancy lower than one year, (excluding HFrEF)
- Recipients of any organ transplant
- Primary significant valve disease (at least moderate to severe valve disease)

**Figure 5:** Inclusion and exclusion criteria in the RocHF-study
ACS: acute coronary syndrome
ESC: European Society of Cardiology
HFrEF: heart failure with reduced ejection fraction
LVEF: left ventricular ejection fraction
NYHA: New York Heart Association
TIA: transient ischemic attack

## *2.3 Assessment of office heart rate*

### 2.3.1 Sitting office heart rate

Blood pressure (BP) and resting heart rate were obtained after at least 5 minutes of rest. The measurements were performed on both arms and then repeated twice on the arm with the initially higher result, with one-minute rest in between each measurement. For further statistical evaluation the mean of all three heart rates was taken.

### 2.3.2 Supine office heart rate

The supine heart rate was automatically determined through a 12-lead ECG during their first visit. This was performed in a quiet room after 5 minutes of rest in a supine position.

## *2.4 Assessment of 24-hours ambulatory blood pressure monitoring (ABPM)*

ABPM was performed using the brachial, oscillometric, automated self-measurement mobil-O-Graph device (I.E.M. GmbH, Stolberg, Germany) with integrated ARCSolver®-Software (Austrian Institute of Technology Wien). The device was validated according to the criteria of the British Hypertension Society (35). The range of measurement is 60–290mmHg for systolic BP, 30–195mmHg for diastolic BP and 30–240 bpm for heart rate.

The ambulatory BP cuff was adjusted correctly on the patient’s non-dominant upper arm after measuring the circumference and using the right size of cuff. An initial measurement was taken after that, whilst instructing the patient to extend his arm during each measurement. After 24 hours of repetitive measurements, the patient was allowed to take off the cuff and switch off ABPM.

Measurements of BP and heart rate were performed every 30 minutes between 10:00pm and 6:00am (nocturnal heart rate (=24hnocHR)) and every 20 minutes between 6:00am and 10:00pm (day heart rate (=24hdayHR)). The overall heart rate measurements will be referred as m24hHR.

## 2.5 Assessment of ejection fraction

The EF was determined through a transthoracic echocardiography. Prior to starting the study, two physicians were chosen to execute this exam, in order to minimize the variance of the collected data.

The ultrasound devices used during this study were a Vivid 7 and a Vivid 9 (GE Healthcare, Chalfont St Giles, UK) with a GE M4S cardiac sector probe (3.5-10 HZ).

The LVEF, the sole echocardiographic parameter used in this work, was evaluated using the Simpson method and automatically calculated using the following formula:

$$\boxed{(LVVed - LVVes)/LVVed \times 100 = EF\ \%}$$

The simultaneously applied ECG was used to define and track the end-diastolic and the end-systolic filling of the left ventricle. The calculated difference between the systolic and diastolic volume of the ventricle is defined as the stroke volume (SV).

In addition to the 2D measurement, a 3D- EF measurement was performed using a GE 4V-D 3-D echo probe.

## 2.6 Assessment of laboratory parameters

Before taking the venous blood sample, the patient was ought to give his/her informed consent and it was verified that the patient was nil by mouth and has taken his/her morning medication as prescribed, as its cofactors could affect the measurements.

Each blood sample was taken between 7am-11am, as to take the circadian rhythm into consideration.

A urine sample was taken from all study patients, and pregnancy tests were performed for each fertile female participant.

The EDTA- blood tubes were immediately put on ice after being filled. All the blood samples were brought to the laboratory right after in order to get the most accurate concentration of all substrates.

In this work the heart failure parameter NT-proBNP was further evaluated.

### 2.6.1 N-terminal pro Brain Natriuretic Peptide (NT-pro BNP)

The concentration of NT-proBNP was determined from the blood plasma of a Lithium-Heparin probe (Vacuette®, Plasma, Lithium Heparin with Separator (Gel), Greiner Bio-One International AG, Frickenhausen, Germany).
It was determined via ECLIA through an Elecsys 2010 (Elecsys Immunoassay Analyzer, Cobas, Roche Diagnostics GmbH, Mannheim, Germany).
The lowest possible measurement of NT-pro BNP was 5pg/ml and came with a standard deviation of 1.8-2.7%, depending on the concentration of NT-proBNP.

## *2.7 Assessment of medication history*

The medical history was assessed through a self-reported medical history, and was documented as follows:

Devices or drugs: names (INNs), dosing scheme (if applicable) and date.

1. Heart failure (medical): Levosimendane, loop diuretics, ACE-inhibitors, angiotensin II receptor I blockers, mineralocorticoid receptor antagonists, neprilysin inhibitors, beta-blockers, ivabradine, digitalis or digoxin, amiodarone, other
2. Coronary artery disease: aspirin, PY12 inhibitors, anti-anginal drugs (nitrates or similar)
3. Others: Pacemaker, oral anticoagulation, heparin, thiazide diuretics, other antihypertensive medication, drugs for psychiatric disorders

### 2.8 Statistics

The statistical evaluation was executed using IBM SPSS statistics 25 (IBM Corporation, Armonk/New York, United States of America). Values of $p < 0.05$ were considered as statistically significant.

Before evaluating and correlating the measurements, the results were graphically and statistically sorted into normally distributed ones and those which did not meet the criteria for normal distribution, using histograms as well as the Kolmogorov-Smirnov Test.
The assumption of a normal distribution was made for m24hHR, m24hdayHR, 3D EF and age. The other parameters like ECG HR, m24hnocHR, office HR, office BP, biplane EF, NT-proBNP and BMI did not fulfill the criteria of normal distribution.
For each subgroup evaluation during the correlation analysis, the parameters were again subdivided into normally distributed ones, and those who did not meet the criteria. This analysis will be assumed as given.

## 3 Results

### 3.1 Subjects

The total number of participants included in this work is 99 (79 males and 20 females), and the gender distribution was as follows: ♂: 79.8% and ♀: 20.2%, with the mean age of 64.8 ± 9.6. Men had a mean age of 65.5 ± 9.3, women were slightly younger, with a mean age of 62.3 ± 10.5, but this was not significant (p=0.190). The oldest subject was 84 for the males, and 80 for females. The youngest participant was 45 in both genders.
The mean BMI in the study population was 29.2 ± 5.3 kg/m². Male participants (N=79) had a slightly lower BMI (28.7 ± 4.7 kg/m²) than female participants (N=20; 30.5 ± 7.3 kg/m²). The highest BMI found in the overall study population was 47.6 kg/m², found in the female subgroup, and the lowest was 15.9 kg/m², from a male participant. The evaluation showed no significant difference in between genders (p=0.440). The prevalence of overweight defined as BMI 25.0–29.9 kg/m² was 80% in both genders, and 35% of patients fulfilled the definition of obesity (BMI > 30 kg/m²) (36).

The overall office BP (N=98) was 126.5 ± 24.6mmHg systolic to 78.4 ± 14.2mmHg diastolic, the highest measurement being 262/130mmHg, the lowest 76/58mmHg, both representatives from the male subgroup.

The mean BP in the female subgroup (N=20) was 119.6 ± 13.4mmHg systolic to 75.9 ± 12.6mmHg diastolic, and in the male subgroup (N=78) it was 128.3 ± 26.5mmHg systolic to 79.0± 14.6mmHg diastolic.

A significant difference in between genders was detected when measuring the systolic BP was taken (p=0.042), whereas the diastolic measurement showed no significant difference (p=0.386).

As expected, NT-proBNP (N=92) was elevated in almost every subject, with an average value of 2317.4 ± 3657.1 pg/ml. The mean NT-proBNP in the female subgroup(N=18) was 1563.4 ± 1935.5 pg/ml, and in the male subgroup(N=74) it was 2500.8 ± 3952.9 pg/ml. Again, no significant difference between genders was noted (p=0.308).

The highest elevation found was 25684.0 pg/ml, in a male subject with an EF of 27%. His office heart rate was 59 bpm, his BP 118/74 mmHg. Unfortunately, there was no 24-hour heart rate measured. The lowest concentration of NT-proBNP recorded was 67.0 pg/ml. This participant was also male and presented himself with an elevated office BP of 165/117 mmHg, and a tachycardia with 91 bpm, which is also found in the mean 24-h measurement. His EF was mildly reduced with a biplane measurement of 41%.

| | **Total (N=99)** | **Female (N=20)** | **Male ( N=79)** |
|---|---|---|---|
| **Age in years** | 65±10 (N=99) | 62±10 (N=20) | 65±9 (N=79) |
| **BMI in kg/m²** | 29±5 (N=99) | 31±7 (N=20) | 29±5 (N=79) |
| **Systole in mmHg** | 127±25 (N=98) | 120±13 (N=20) | 128±27 (N=78) |
| **Diastole in mmHg** | 78±14 (N=98) | 76±13 (N=20) | 79±15 (N=78) |
| **NTproBNP in pg/mL** | 2317.4±3657.1 (N=92) | 1563.4±1935.5 (N=18) | 2500.8±3952.9 (N=74) |

**Table 1:** Demography of the study population
BMI: body mass index
N: number of patients

## 3.2 Heart failure medication

The HF medication was assessed as described in chapter 2.7.

A β-blocker was taken by 94%, with bisoprolol being the one most commonly used (76%). Aldosterone-antagonists where given to 72% of all people followed by ACE-inhibitors (50%), where lisinopril was given most often (52%). AT1-blockers were given to 42% and sacubitril-valsartan was given to 21%. Calcium-antagonists were given to 6% of the patients.

As antiarrhythmic drugs, amiodarone (13%) and glycosides (12%) were documented.

According to the patients' medical history, a loop diuretic was given to 62% of all patients, 7% had thiazide and other diuretics were given in 9% of all HF-patients.

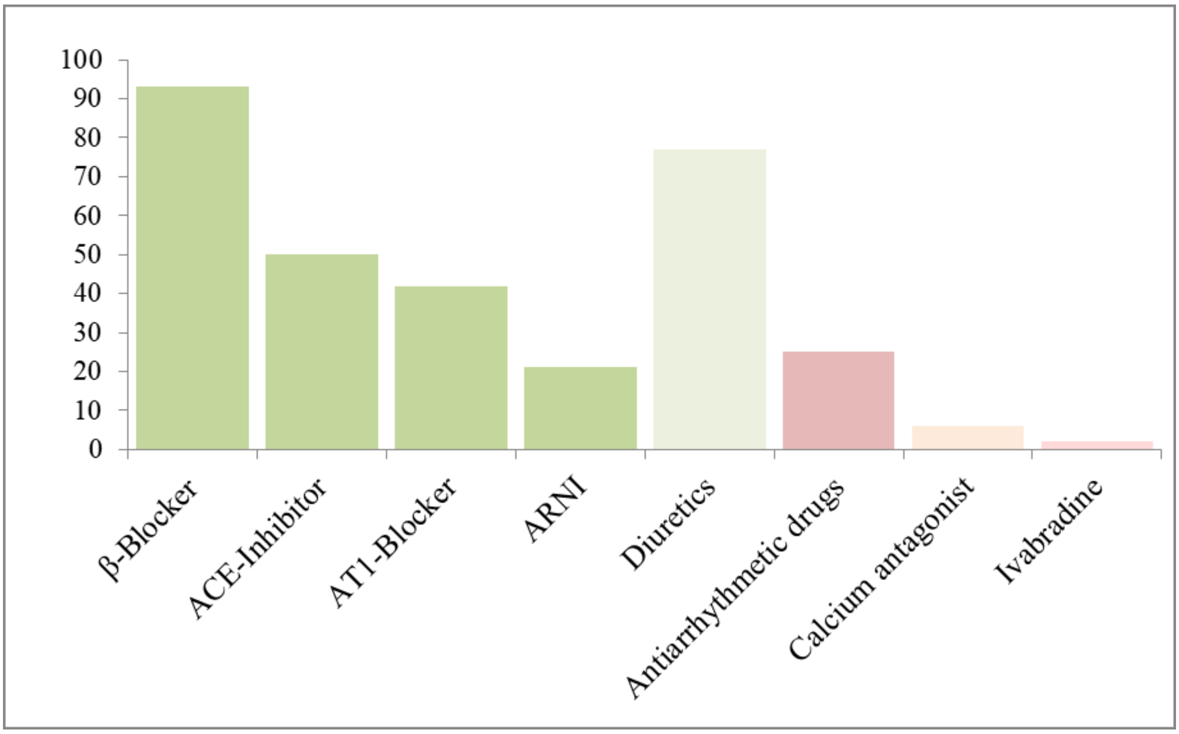


**Figure 6:** Pharmacological HF treatment in percent in study population

### *Optimal heart failure treatment*

The optimal HF treatment was evaluated in the cohort subgroup with patients who had an EF ≤ 35% (N=51). The mean EF in this subgroup was 28.6±6.4%.

The optimal treatment includes an ACE-inhibitor, a β-Blocker as well as a MR antagonist (37). 72.5% (N=37) met these criteria, 96% (N=49) got at least 2 out of 3 substance groups mentioned above.

## 3.3 Ejection fraction

The mean biplane EF was available in all patients (N=99) and was 35.1 ±9.0%, slightly higher in the female subgroup with 39.1±6.7% compared to the males with 34.1±9.3%. The lowest and highest biplane EF measurement was both found in males with 12% and 59%, respectively. 69% of all participants had an ejection fraction <40%. An EF ≤ 35% was present in 52% (N=51) of the patients. One participant presented with a normal ejection fraction with a measurement of 59%, but was not excluded, as he had a 3D EF of 49% and an elevation of NT-proBNP of 238 pg/ml.

It was only possible to evaluate 62 (=63%) measurements of 3D- EF, due to inadequate image quality in a certain proportion of patients. The mean 3D- EF was slightly lower overall with 33.9±10.4% and in both genders for female: 36.6±9.5%, for males: 33.4±10.6%. Both extremes were again found in the male subgroup, with 15% being the lowest and 55% being the highest. Again, the participant with the highest 3D- EF was not excluded due to a biplane measurement of 43%. And again, 63% of the valid measurements showed an EF of <40%, and 52% with an EF ≤ 35%.

A significant difference in between genders was detected, when measuring the biplane EF (p=0.028), whereas there was no difference in the measurement of 3D- EF (p=0.333).

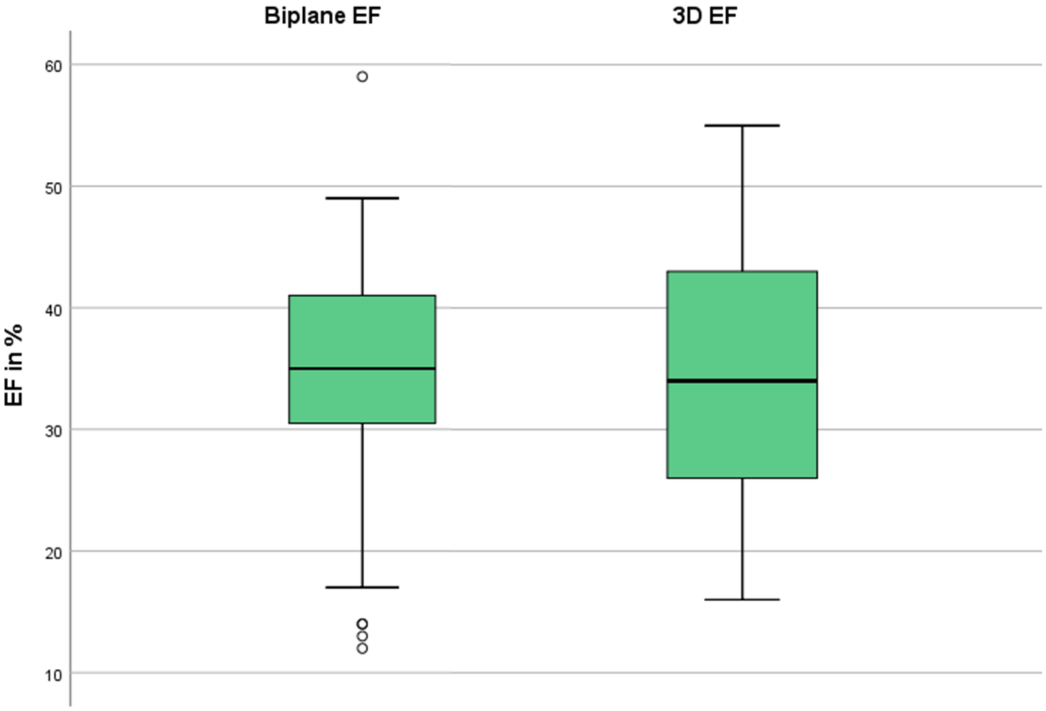


**Figure 7:** Boxplot: Biplane EF of 99 patients with a mean of 35.1 ±9.0% and 3D EF of 62 patients with a mean of 34.1±9.3%. Significant correlation between the two measurements (p<0.001)

## 3.4 Heart rate and correlations within the measurements

During the study, different measurements of heart rates were performed on each study subject.

As described in the chapters before, the heart rate was collected during the ECG measurements, performed in supine position as well as during BP measurements in sitting position (measured 3 times, then the mean value was calculated) and during a 24-hour-ambulatory BP measurement (=m24hHR). The last category was then subdivided into day (=24hdayHR) and night (10pm-6am, =24hnocHR) measures, in order to collect heart rate measures during the presumed resting phase of the patients. There was no significant difference in between genders in all measurements (ECG HR: p=0.260; mean office HR: p=0.602; m24HR: p=0.408; m24hdayHR p=0.507 and m24hnocHR p=0.274)

The mean ECG heart rate (N=98) was 71.9±15.9 bpm, with a minimum of 44 bpm and a maximum of 129 bpm, both representatives from the male subgroup, where the mean HR was 73.0±16.9 bpm. For the female subgroup the mean HR was 67.6±10.8bpm.

For mean office heart rate (N=97) 3 measurements were performed for each patient after that the average was calculated. It was 68.5 ± 13.3 bpm, for the female subgroup slightly below that with 67.7±14.8 bpm and for male subjects slightly above average with 68.7±12.9 bpm. The overall highest was 108 bpm, the lowest 48bpm.

The overall ABPM-measurements (N=94) showed a mean of 68.3±10.9 bpm, 70.1±11.6 bpm for females and 67.8±10.7 bpm for males. The maximum was 103bpm, minimum was 47 bpm.

The m24hdayHR (N=93) was 70.3±10.9 bpm, for females 72.7±11.4 bpm and for males 69.8±10.8 bpm. Both extremes were again found in the male subgroup, with 50 bpm being the lowest and 103 bpm being the highest HR.

The m24hnocHR (N=90) was 63.8±10.7 bpm, for females 66.6±12.3 bpm, for males 63.2±10.2 bpm. As in all other measurements, the minimum (42 bpm) and maximum (92 bpm) were found in the male subgroup.

Connections within the different measurements of heart rate have been found.

Non-surprisingly, the m24hHR correlated strongly with the m24hdayHR (N=93, Pearson=0.973, p<0.001) and the m24hnocHR (N=90, Spearman=0.890, p=0.000).

The office HR correlated best with the 24hdayHR (N=91, Spearman=0.723, p<0.001), followed by the m24hHR (N=92, Spearman=0.686, p<0.001) and 24hnocHR (N=88, Spearman=0.573, p<0.001).

On the other hand, it was observed, that the ECG-heart rate did not seem to correlate with any other HR measurements:

m24hHR: (N=93, Spearman=0.131, p=0.209), m24hdayHR: (N=92, Spearman=0.131, p=0.213), m24hnocHR (N=89, Spearman=0.125, p=0.243) and officeHR: (N=96, Spearman=0.086, p=0.405).

For further analysis, patients were subdivided into those who presented with AF, those who had a pacing device stimulating the right ventricle and those, who presented with none of the above, presuming a sinus rhythm.

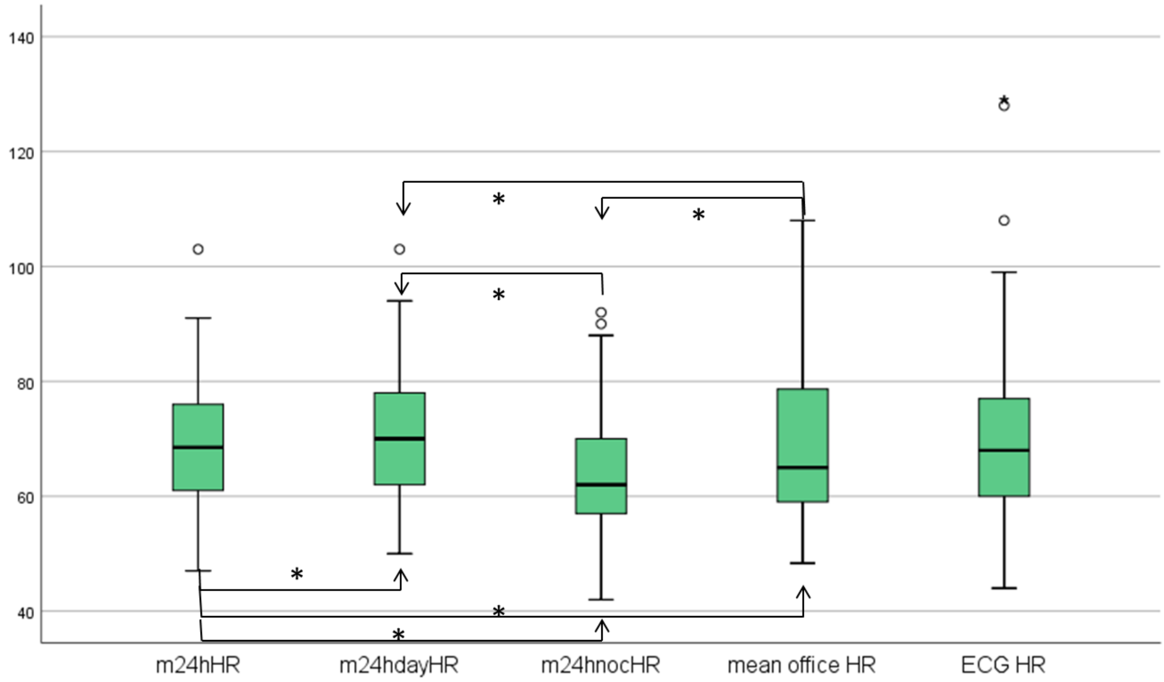


**Figure 8:** Displaying significant correlations (=*) between different HR measurements

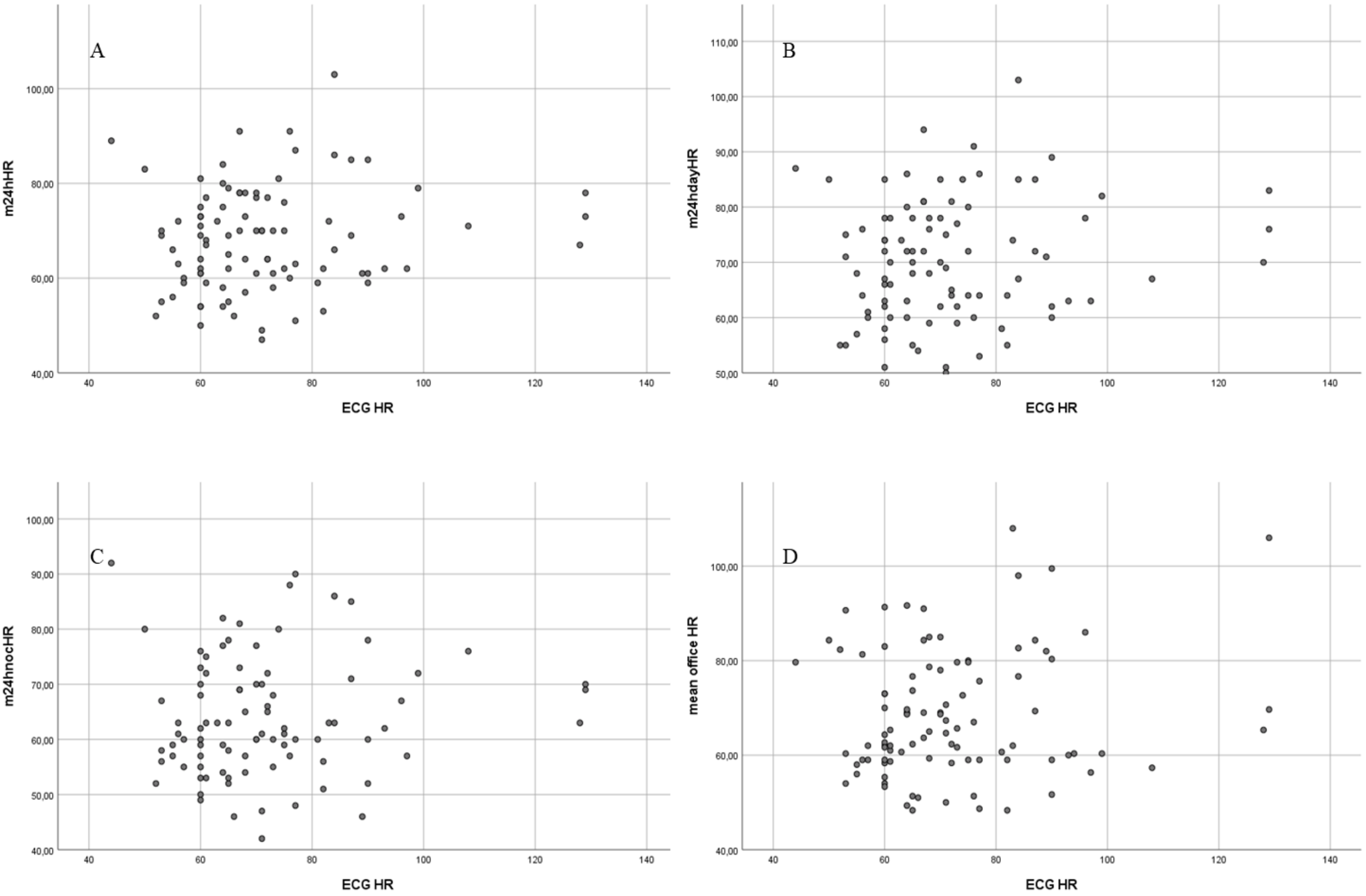


**Figure 9:** Scatterplot: displaying missing correlation between ECG HR and other HR measurements

A) ECG HR and m24hHR p=0.209
B) ECG HR and m24hdayHR p=0.213
C) ECG HR and m24hnocHR p=0.243
D) ECG HR and mean office HR p=0.405

### 3.4.1 Presumed sinus-rhythm and heart rate

All patients, who did not have a pacing device or signs of AF were accounted in this subgroup (N=44). The office HR (N=44) was 68.7±14.0 bpm and the mean ECG HR (N=43) was 69.7±14.1 bpm. The mean ambulatory measurements were 69.3±10.4 bpm for m24hHR (N=42), for 24hdayHR (N=43) they were 69.9±9.6 bpm and for 24hnocHR (N=41) they were 63.4±11.9 bpm.

The ambulatory HR measurements were found to strongly correlate with each other (m24hHR with m24hdayHR p<0.001; m24hHR with m24hnocHR p<0.001; m24hdayHR with m24hnocHR p<0.001), while the two measurements executed during the ambulatory visit did not correlate with any other measurement: The correlation analysis for the mean office HR measurements was as follows: m24hHR p=0.943, m24hdayHR p=0.735, m24hnocHR p=0.219, ECG HR p=0.126; and for ECG HR it was m24hHR p=0.378, m24hdayHR p=0.395, m24hnocHR p=0.391.

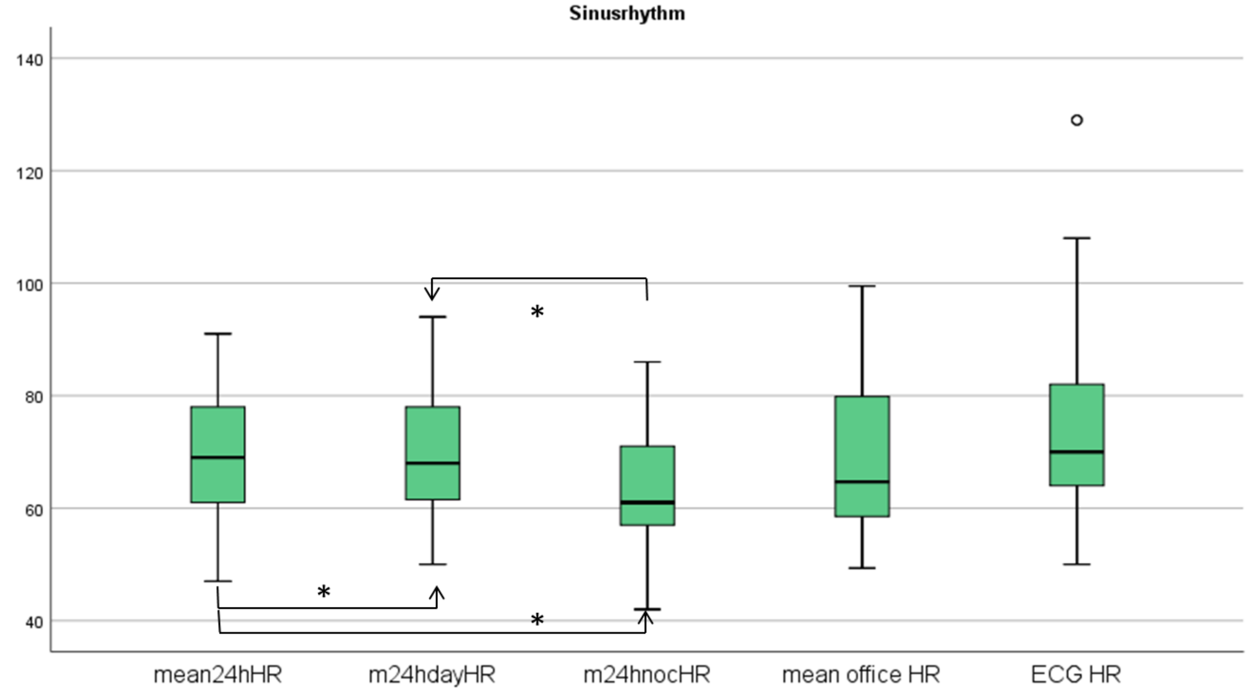


**Figure 10:** Displaying significant correlations (=*) between different HR measurements in the subgroup of patients presenting with a sinus rhythm

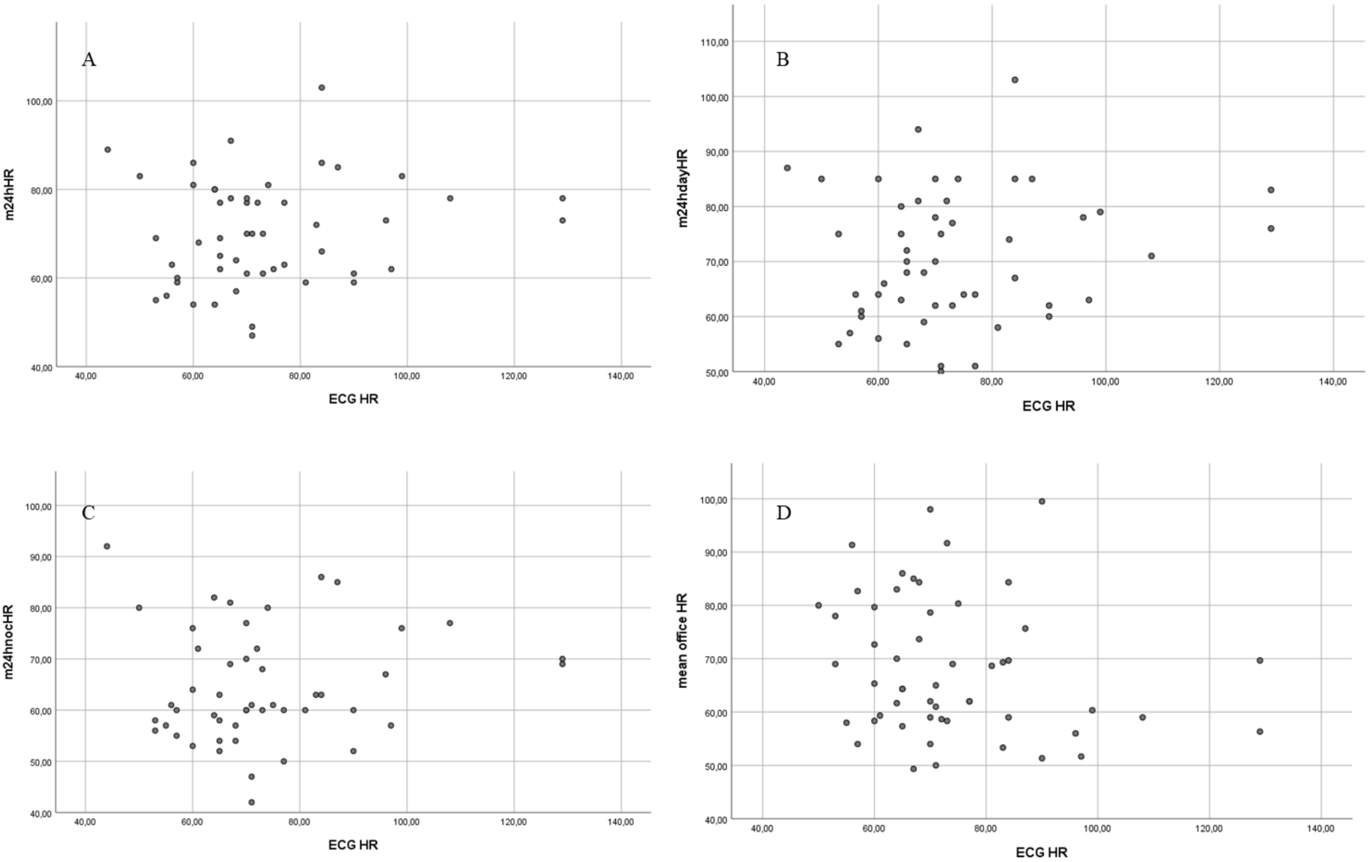


**Figure 11:** Scatterplot: sinus rhythm
Displaying missing correlation between ECG HR and other HR measurements

A) ECG HR and m24hHR p=0.378
B) ECG HR and m24hdayHR p=0.395
C) ECG HR and m24hnocHR p=0.391
D) ECG HR and mean office HR p=0.126

### 3.4.2 Pacing device and heart rate

18 patients in total were found to have a pacing device actively stimulating the right ventricle. In this subgroup the m24hHR was (N=17): 69.8±12.0 bpm, m24hnocHR (N=16): 65.2±14.7 bpm and m24hdayHR (N=17) was 71.2±11.3 bpm.

The office heart rate (N=18) was 63.9±13.0 bpm and the ECG heart rate (N=18) was 69.8±10.6 bpm.

When performing a correlation analysis, the ambulatory HR measurements correlated strongly with each other (m24hHR with m24hdayHR $p<0.001$; m24hHR with m24hnocHR $p<0.001$; m24hdayHR with m24hnocHR $p<0.001$), but the other measurements, namely the mean office HR (m24hHR $p=0.251$, m24hdayHR $p=0.436$, m24hnocHR $p=0.688$, ECG HR $p=0.917$) and the ECG HR (m24hHR $p=0.946$, m24hdayHR $p=0.969$, m24hnocHR $p=0.816$) did not correlate with the other HR measurements.

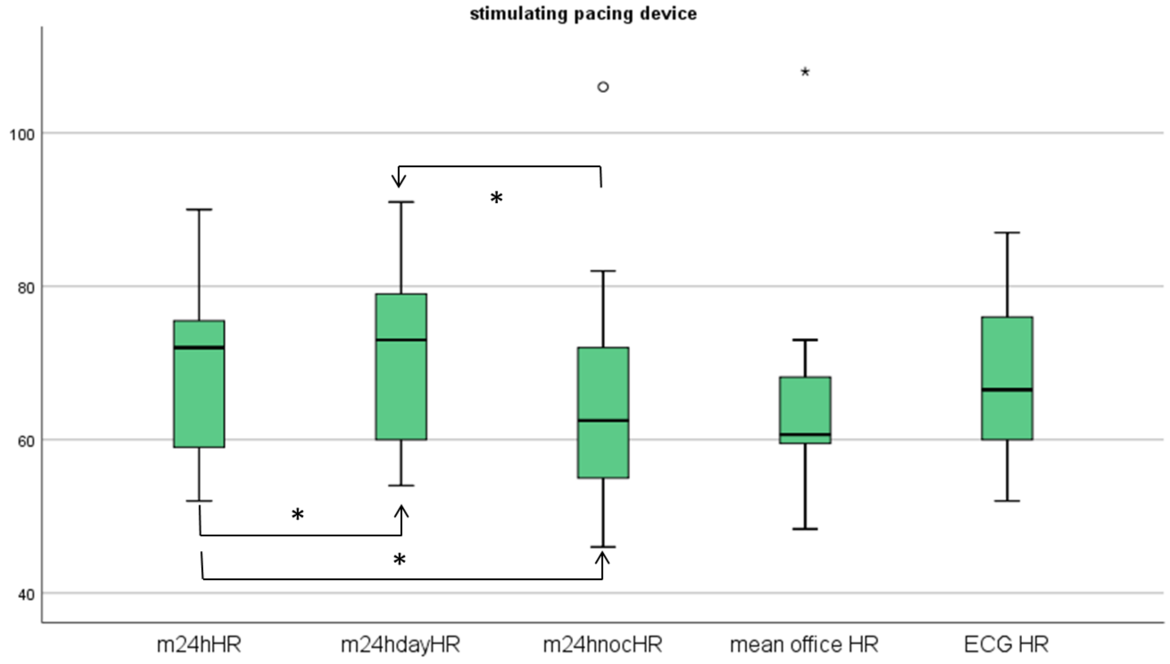


**Figure 12:** Displaying significant correlations (=*) between different HR measurements in the subgroup of patients presenting with a stimulating pacing device

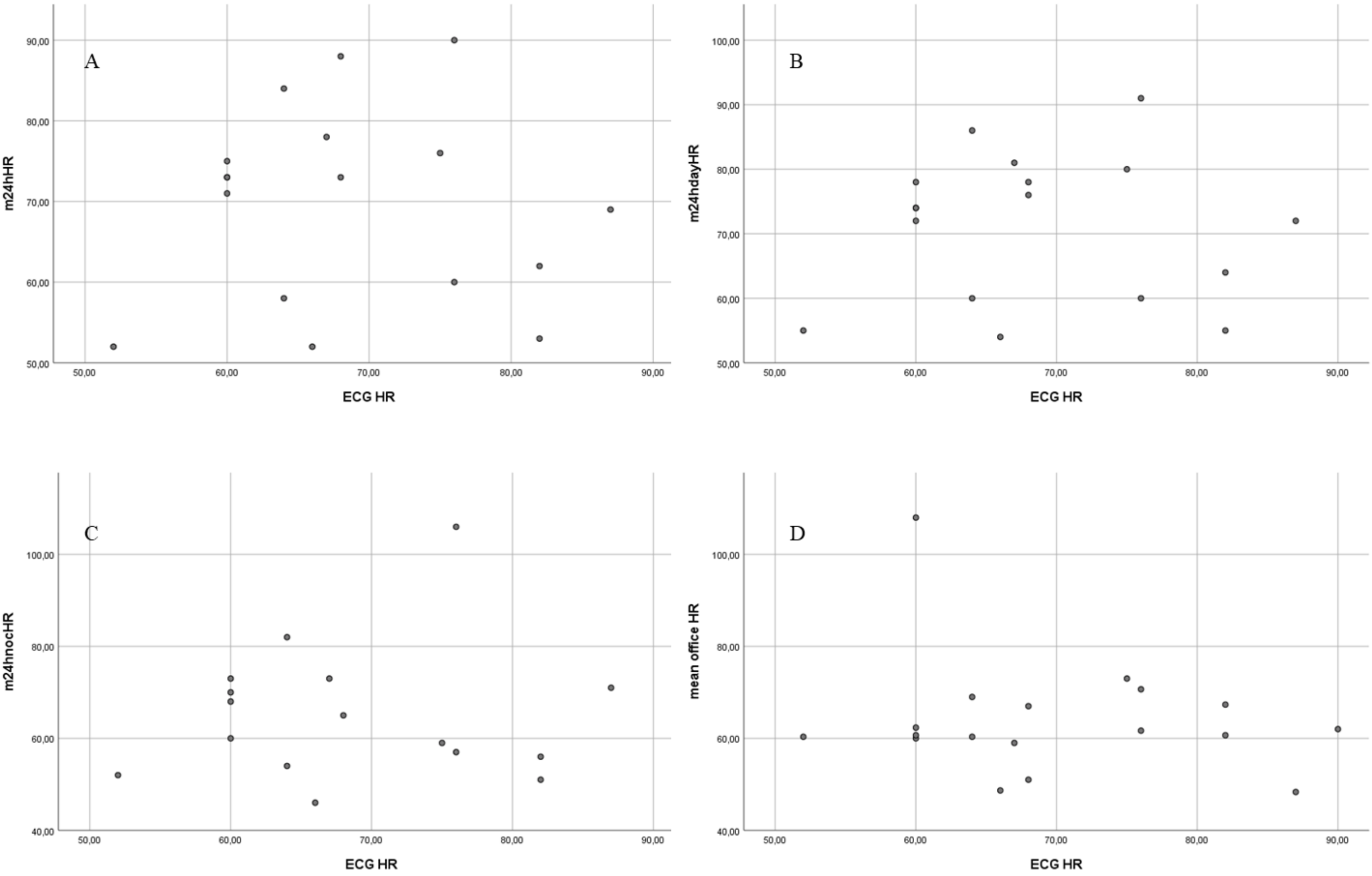


**Figure 13:** Scatterplot: pacing device:
displaying missing correlation between ECG HR and other HR measurements

A) ECG HR and m24hHR p=0.946
B) ECG HR and m24hdayHR p=0.969
C) ECG HR and m24hnocHR p=0.816
D) ECG HR and mean office HR p=0.917

### 3.4.3 Arrhythmia and heart rate

AF was noted in 34% (N=34) of all participants the 12-lead-ECG, 6 of receiving at least one antiarrhythmic drug.

The average heart rate in the subgroup of patients with AF was as follows:

The m24hHR was (N=33): 69.1±10.1 bpm, m24hnocHR (N=33): 64.55±12.6 bpm and m24hdayHR (N=34) was 69.5±9.6 bpm.

The office heart rate (N=34) was 70.6±15.1 bpm and the ECG heart rate (N=33) was 69.6±14.8 bpm.

When correlating the different HR measurements in this subgroup, the ambulatory HR measurements correlated strongly with each other (m24hHR with m24hdayHR $p<0.001$; m24hHR with m24hnocHR $p<0.001$; m24hdayHR with m24hnocHR $p<0.001$) whereas the mean office HR did not correlate with any other measurements (m24hHR $p=0.528$, m24hdayHR $p=0.175$, m24hnocHR $p=0.543$, ECG HR $p=0.131$) and nor did the ECG-HR (m24hHR $p=0.315$, m24hdayHR $p=0.474$, m24hnocHR $p=0.320$)

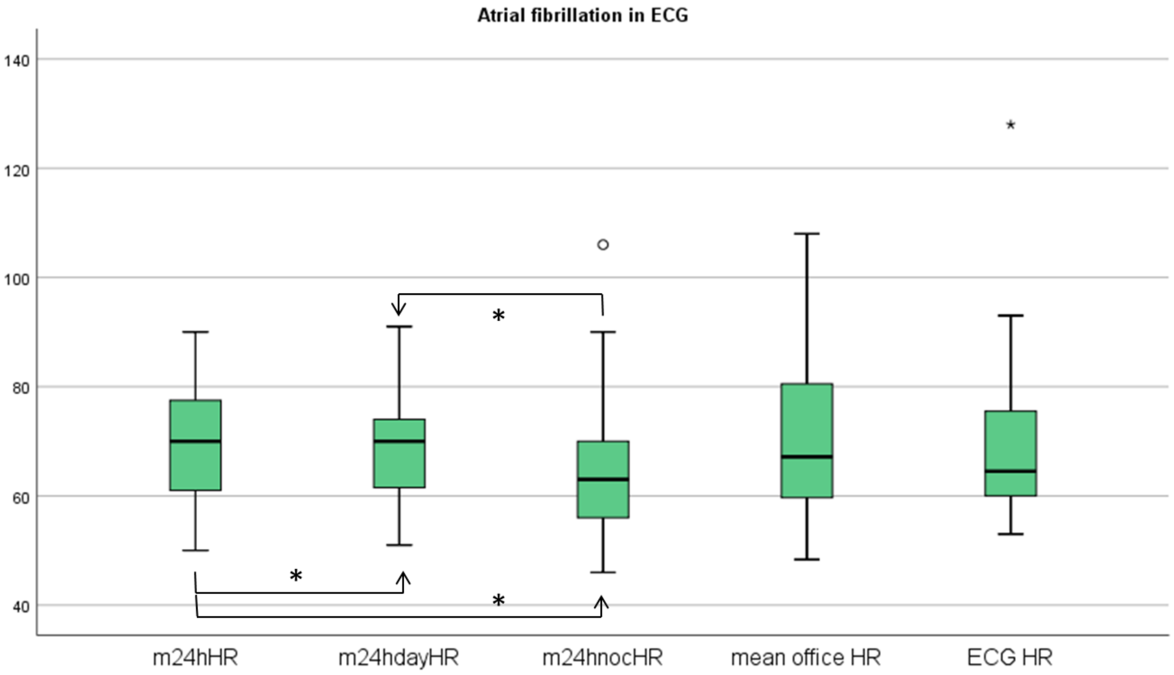


**Figure 14:** Displaying significant correlations (=*) between different HR measurements in the subgroup of patients presenting with atrial fibrillation during a 12-lead ECG

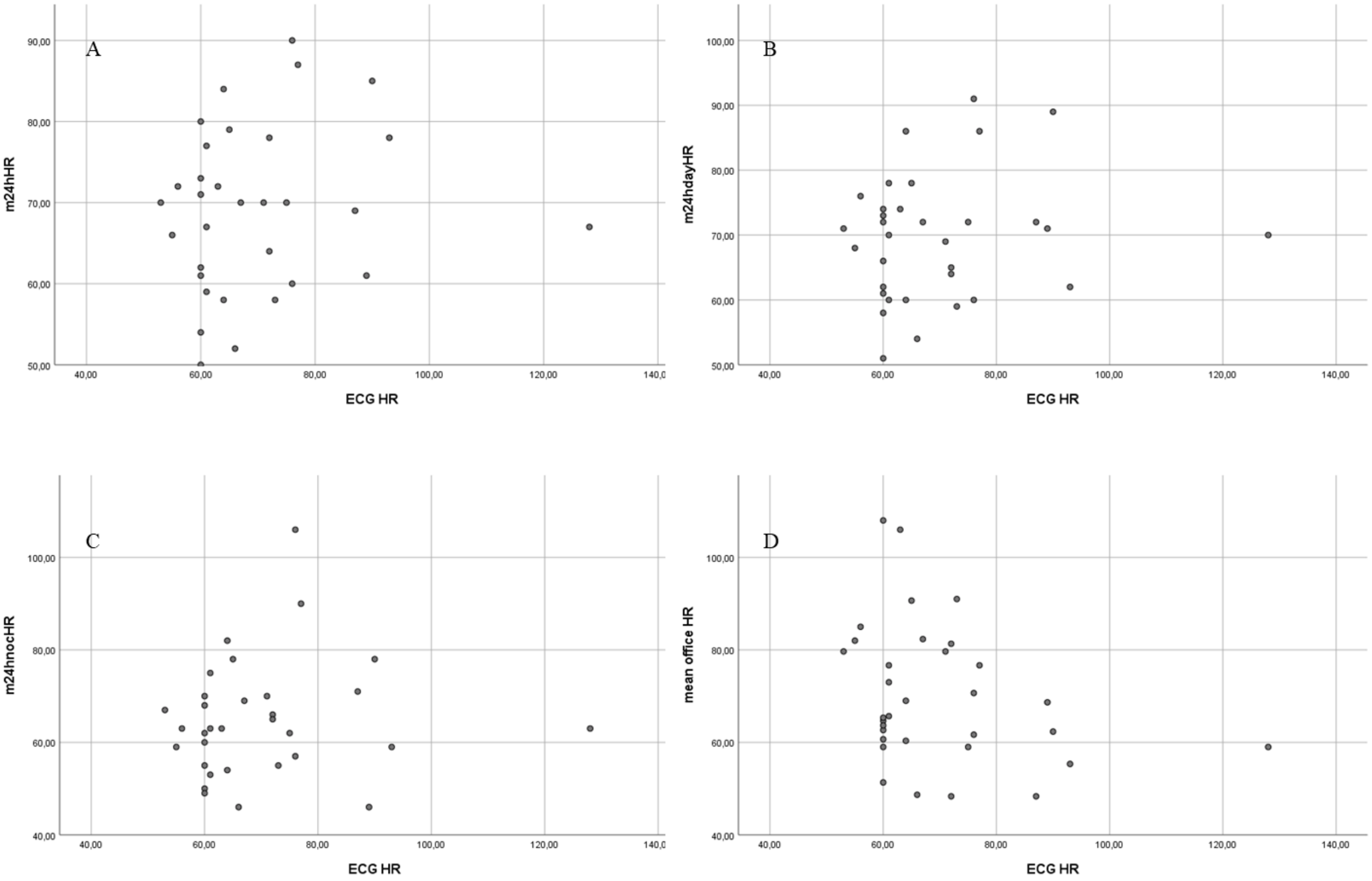


**Figure 15:** Scatterplot: atrial fibrillation: displaying missing correlation between ECG HR and other HR measurements

A) ECG HR and m24hHR p=0.315
B) ECG HR and m24hdayHR p=0.474
C) ECG HR and m24hnocHR p=0.320
D) ECG HR and mean office HR p=0.131

## 3.5 Correlation analysis

To assess possible correlations between different parameters, correlation analyses were performed.

The following parameters were included in that relation: all HR measurements, office BP measurement, biplane EF, 3D EF, NT-proBNP, age and BMI.).

### *NT-proBNP*

NT-proBNP was found to significantly correlate with both the biplane EF (Spearman r=-0.268, p=0.010) and the 3D EF measurement (Spearman r=-0.412, p=0.001), whereas no significant correlation was found when looking at the heart rate measurements: m24hHR (Spearman r=-0.097, p=0.370), m24hdayHR (Spearman r=-0.091, p=0.403), m24hnocHR (Spearman r=-0.079, p=0.477), office HR (Spearman r=0.080, p=0.456) and ECG HR (Spearman r=-0.058, p=0.582)

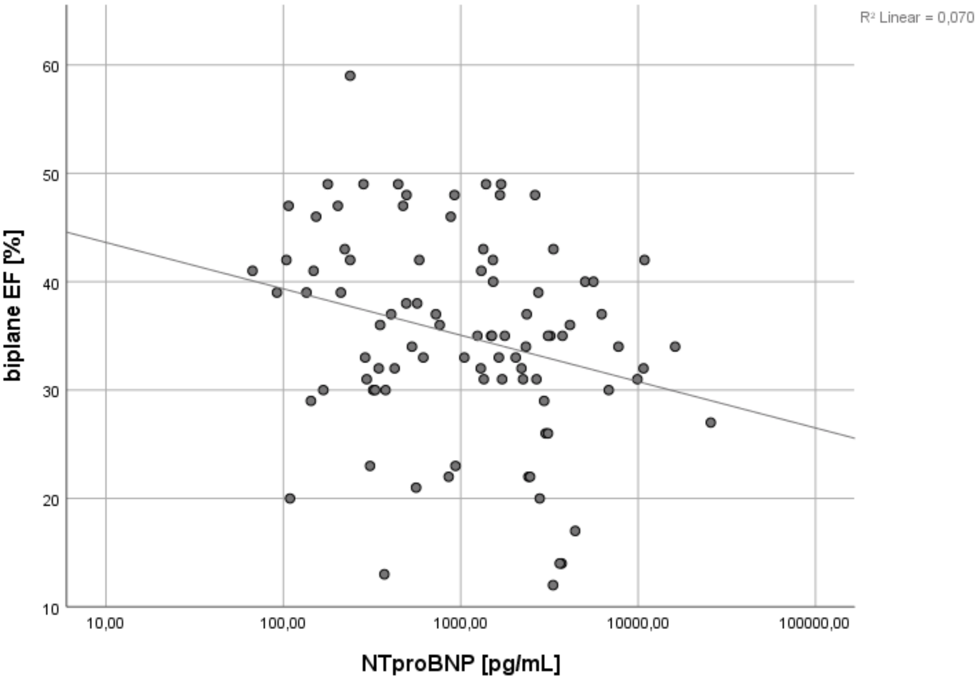


**Figure 16:** Scatterplot. x-axis: NT-proBNP [pg/mL], y-axis: biplane EF [%]. Significant negative correlation between NT-proBNP and the biplane EF: Spearman r=-0.268, p=0.010

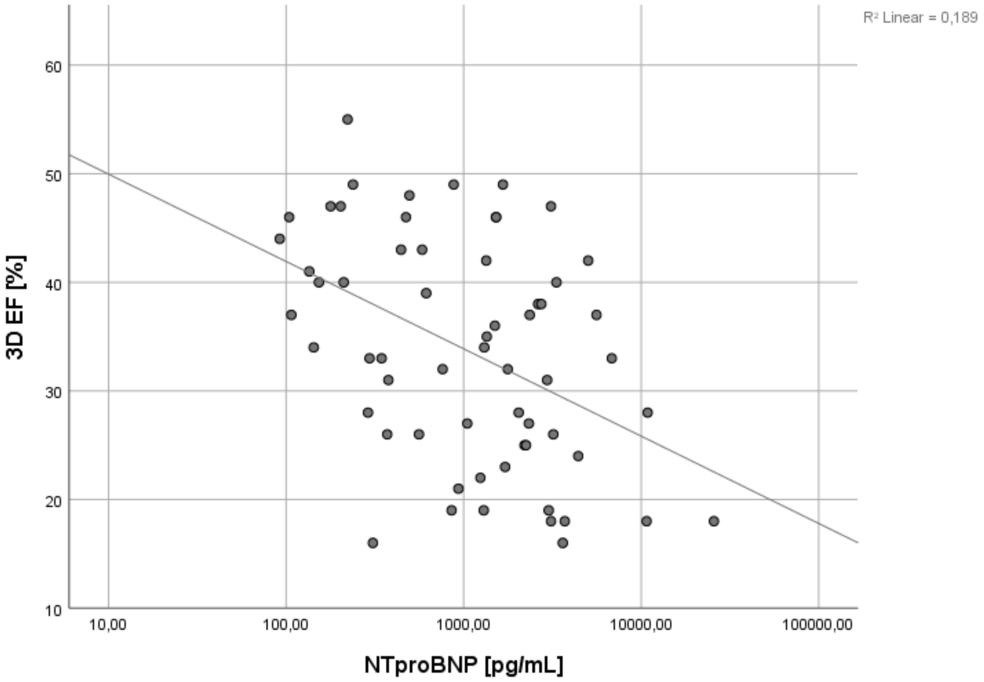


**Figure 17:** Scatterplot. X-axis: NT-proBNP [pg/mL], y-axis: biplane EF [%]. Significant negative correlation between NT-proBNP and the 3D EF: Spearman r=-0.412, p=0.001

### *Age*

Age did not seem to correlate with neither the biplane EF measurement (Spearman r= 0.185, p=0.185) nor the 3D EF measurement (Pearson r=0.206, p=0.109).

When looking at the heart rate measurements, a negative correlation was found between age and the following ambulatory heart rate measurements: m24hHR (Pearson r=-0.276, p=0.007), m24hdayHR (Pearson r=-0.240, p=0.021). No correlation was found when looking at m24hnocHR (Spearman r=-0.190 p=0.073), office HR (Spearman r=-0.033, p=0.751) and ECG HR (Spearman r=0.079, p=0.438)

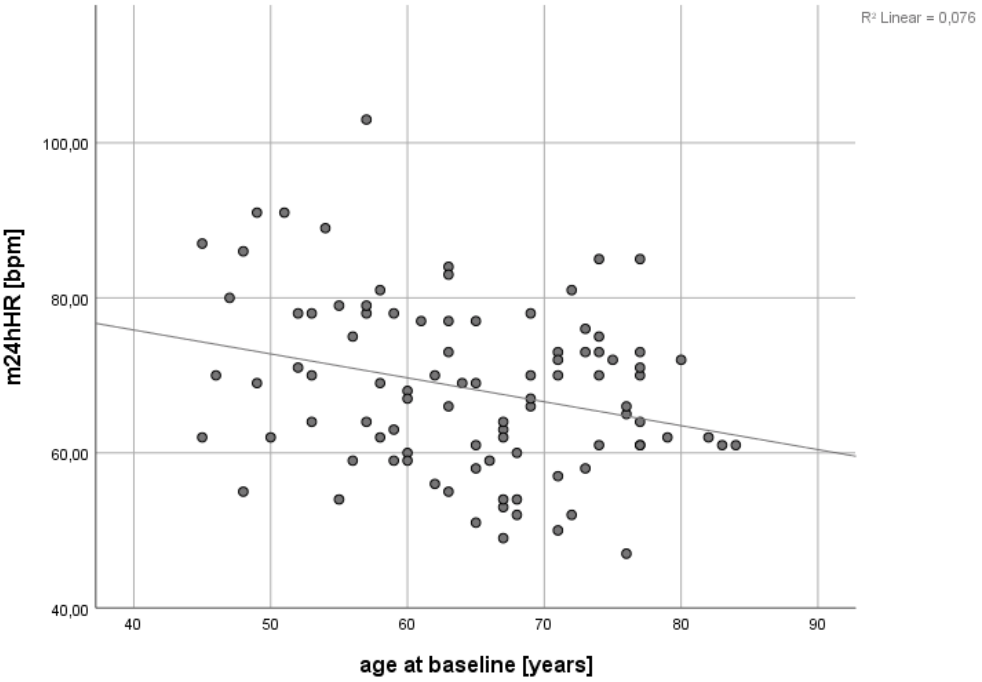


**Figure 18:** Scatterplot. X-axis: Age at baseline [years], y-axis: m24hHR [bpm]. Significant negative correlation, Pearson r=-0.276, p=0.007

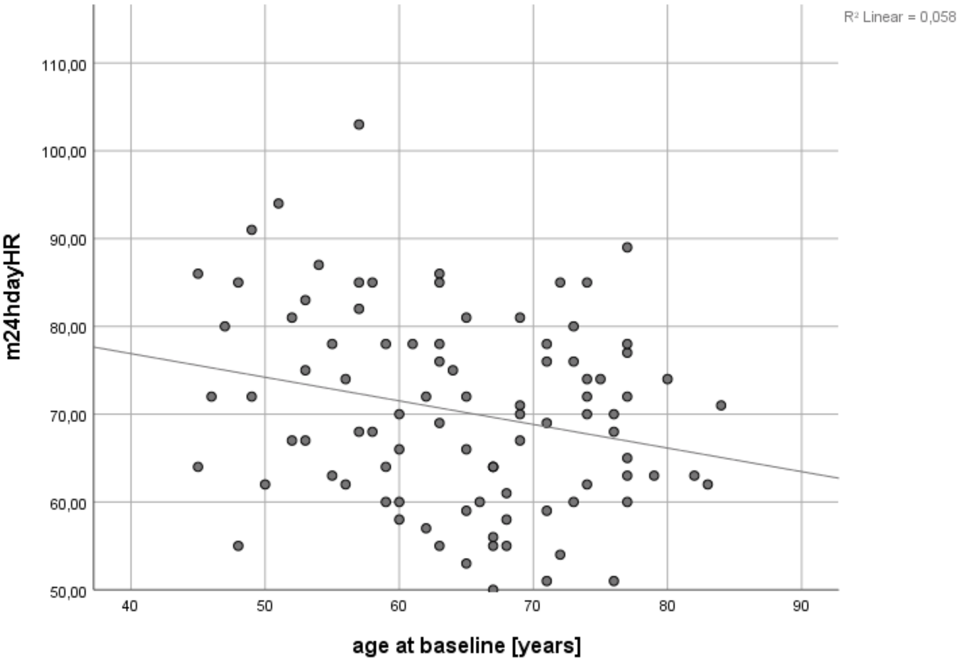


**Figure 19:** x-axis: Age at baseline [years], y-axis: m24hdayHR [bpm]. Significant negative correlation, Pearson r=-0.240, p=0.021

*BMI*

The BMI did not correlate with both the biplane EF (Spearman r=-0.156, p=0.271) and the 3D measurement (Spearman r=-0.111, p=0.434).

The following HR measurements correlated with the BMI: m24hHR (Spearman r=0.289, p=0.038), m24hdayHR (Spearman r=0.363, p=0.008), office HR (Spearman r=0.306, p=0.028). The BMI did not correlate with the m24hnocHR (Spearman r=0.216, p=0.123) and the ECG HR (Spearman r=-0.147, p=0.298).

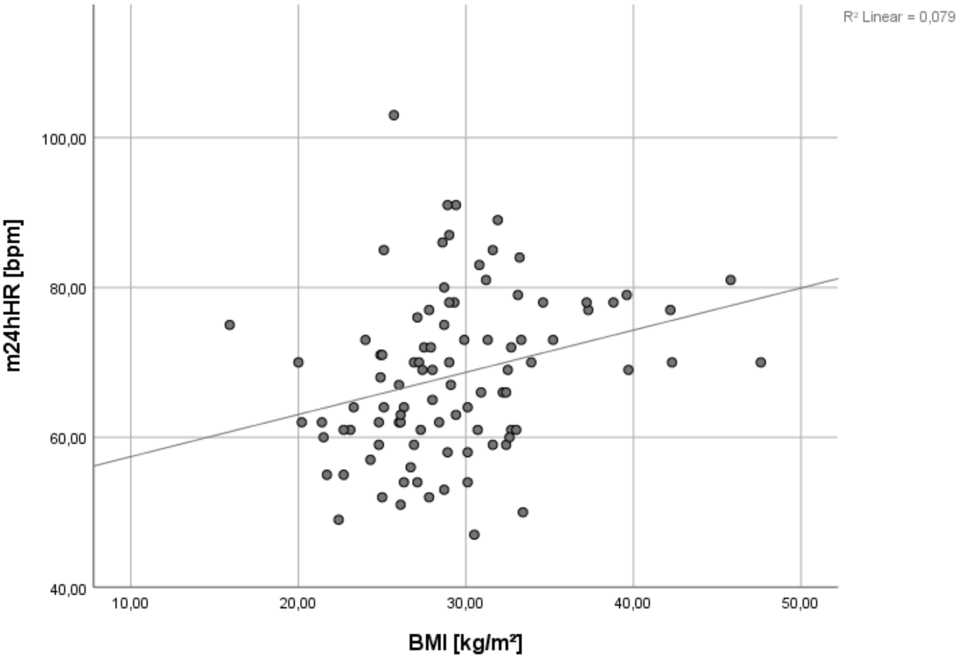


**Figure 20:** X-axis: BMI [kg/m²], y-axis: m24hHR [bpm]. Significant correlation, Spearman r=0.289, p=0.038

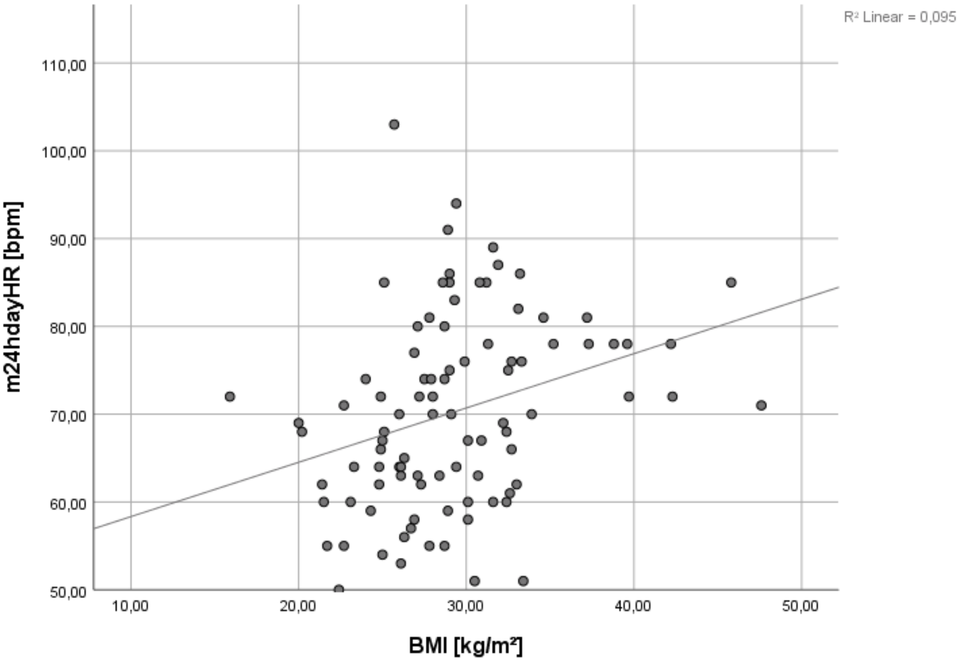


**Figure 21:** X-axis: BMI [kg/m²], y-axis: m24hdayHR [bpm]. Significant correlation, Spearman r=0.363, p=0.008

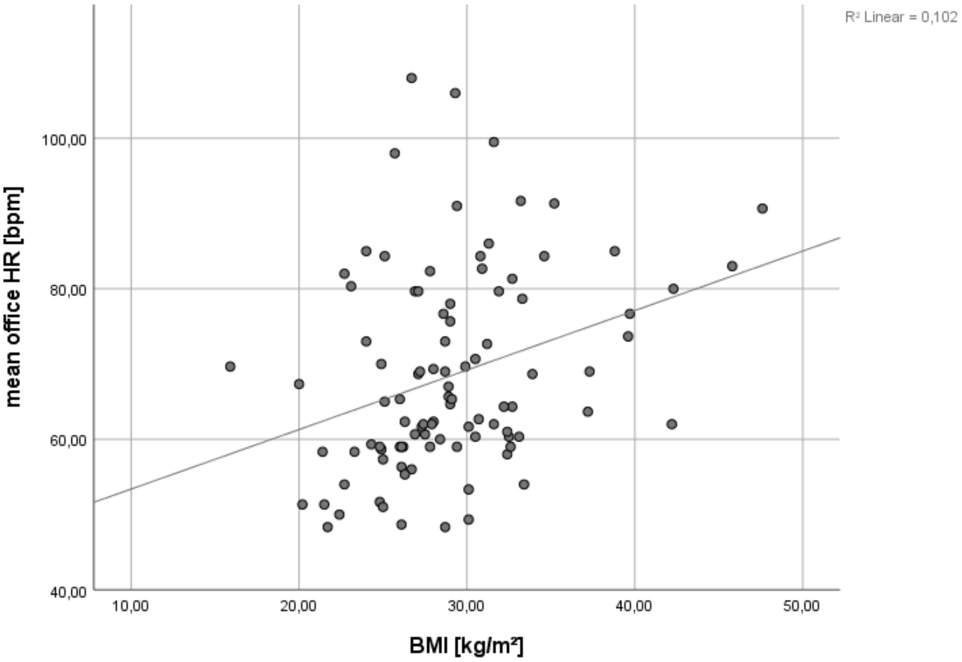


**Figure 22:** X-axis: BMI [kg/m²], y-axis: mean office HR [bpm]. Significant correlation, Spearman r=0.306, p=0.028

### *Blood pressure*

The office systole correlated strongly with the measured office diastole (Spearman r=0.720 p <0.001).

The office BP did not correlate with the biplane ((Systole: Spearman r=-0.051 p=0.719), (Diastole: Spearman r=-0.161, p=0.255)) and the 3D EF measurement ((Systole: Spearman r=0.072, p=0.611), (Diastole: Spearman r=-0.036, p=0.798)).

The BP did not correlate with any HR measurement: m24hHR ((Systole: Spearman r=-0.176, p=0.211), (Diastole: Spearman r=0.159, p=0.261)), m24hdayHR ((Systole: Spearman r=-0.165, p=0.243), (Diastole: Spearman r=0.132, p=0.350)), m24hnocHR ((Systole: Spearman r=-0.183, p=0.195), (Diastole: Spearman r=0.222, p=0.113)), officeHR ((Systole: Spearman r=-0.025, p=0.862), (Diastole: Spearman r=0.087, p=0.542)) and ECG HR ((Systole: Spearman r=0.093, p=0.513), (Diastole: Spearman r=-0.005, p=0.970)).

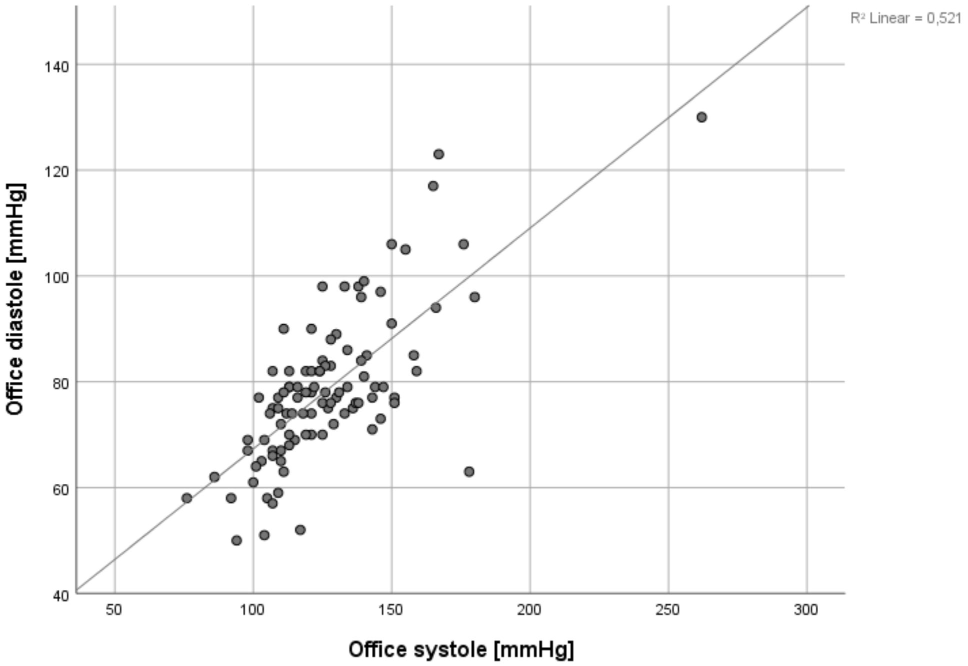
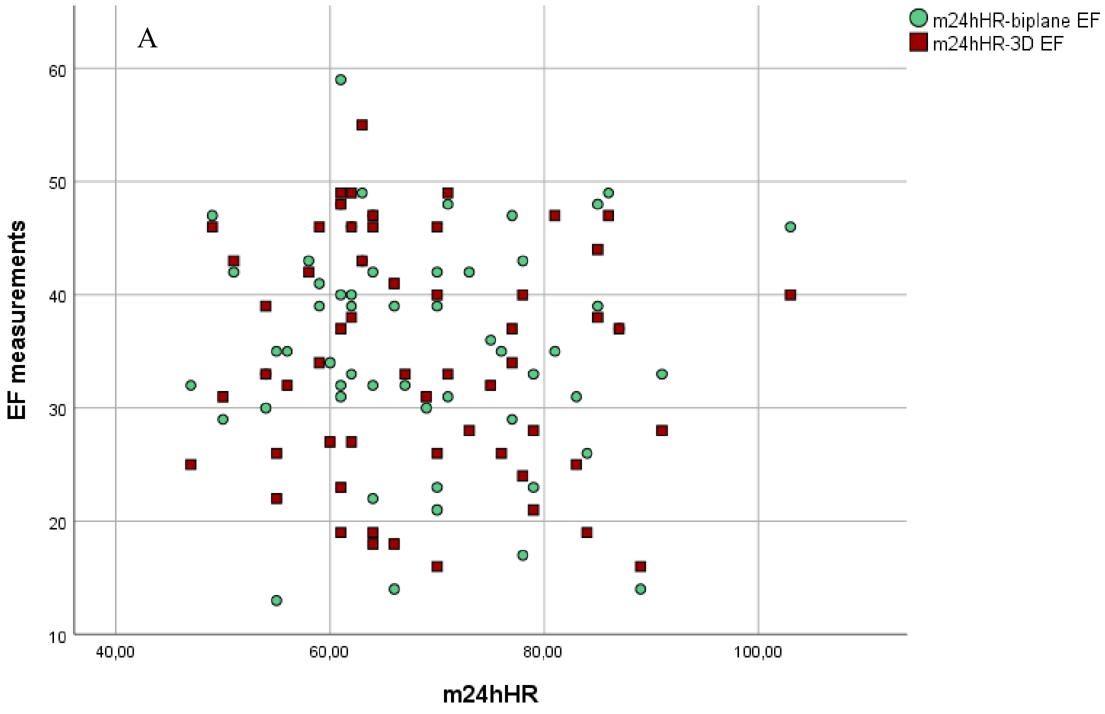


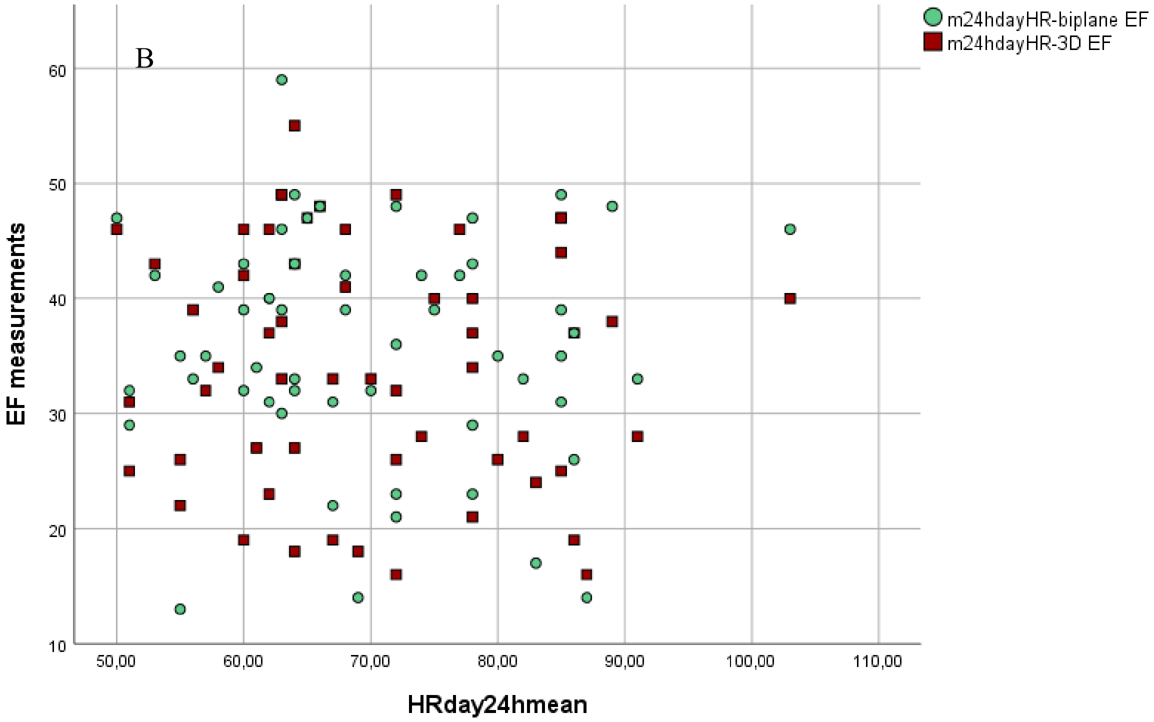
**Figure 23:** X-axis: mean office systole [mmHg], y-axis: mean office diastole [mmHg]. Significant correlation, Spearman r=0.720, p<0.001

### 3.5.1 EF in correlation to heart rate

First, the two different EF measurements were evaluated and as suspected, they correlate strongly (Spearman r=0.830, p<0.001).

Following results were found for the biplane measurements when being correlated to the different heart rate measurements: m24hHR (Spearman r=0.013, p=0.905), m24hdayHR (Spearman r=0.018, p=0.866), m24hnocHR (Spearman r=-0.064, p=0.549), ECG HR (Spearman r=0.082, p=0.424) and officeHR (Spearman r=-0.175, p=0.350).
When looking at the 3D measurements, similar results were found: m24hHR (Pearson r=-0.091, p=0.503), m24hdayHR (Pearson r=-0.072, p=0.600), m24hnocHR (Spearman r=-0.103, p=0.457) and officeHR (Spearman r=-0.175, p=0.178), ECG-HR (Spearman r=0.030, p=0.818).
For more precise results, the study group was again subdivided into the following groups:




B
m24hdayHR-biplane EF
m24hdayHR-3D EF
EF measurements
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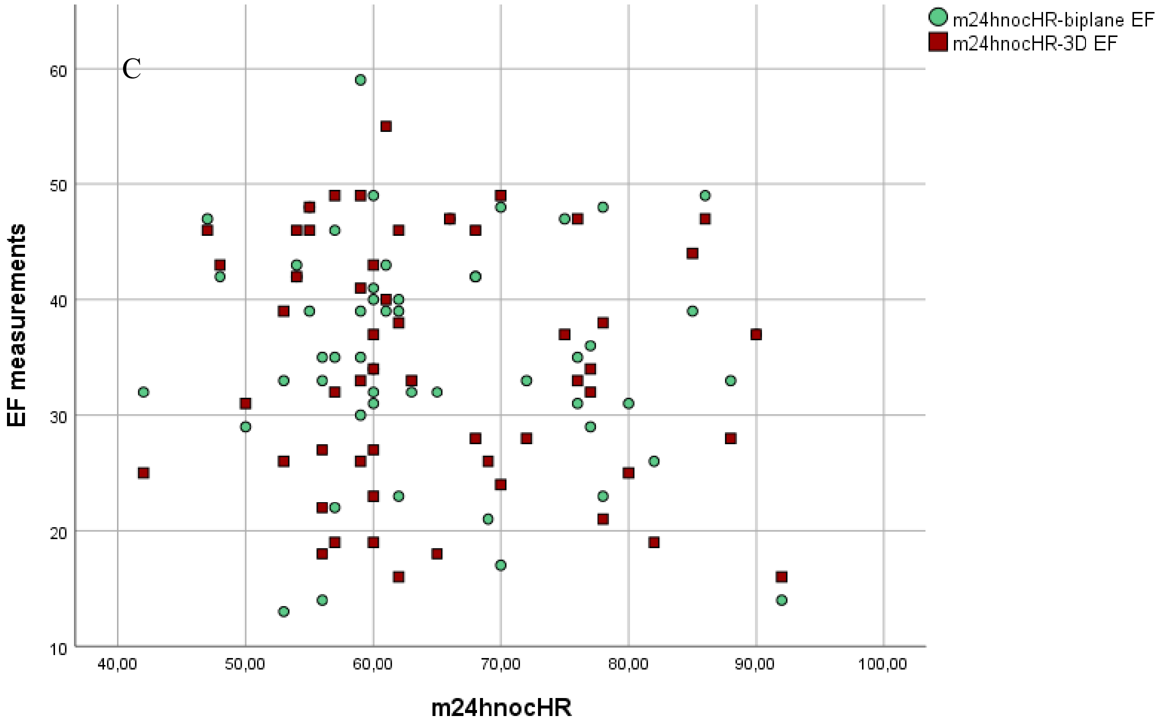
HRday24hmean


C
m24hnocHR-biplane EF
m24hnocHR-3D EF
EF measurements
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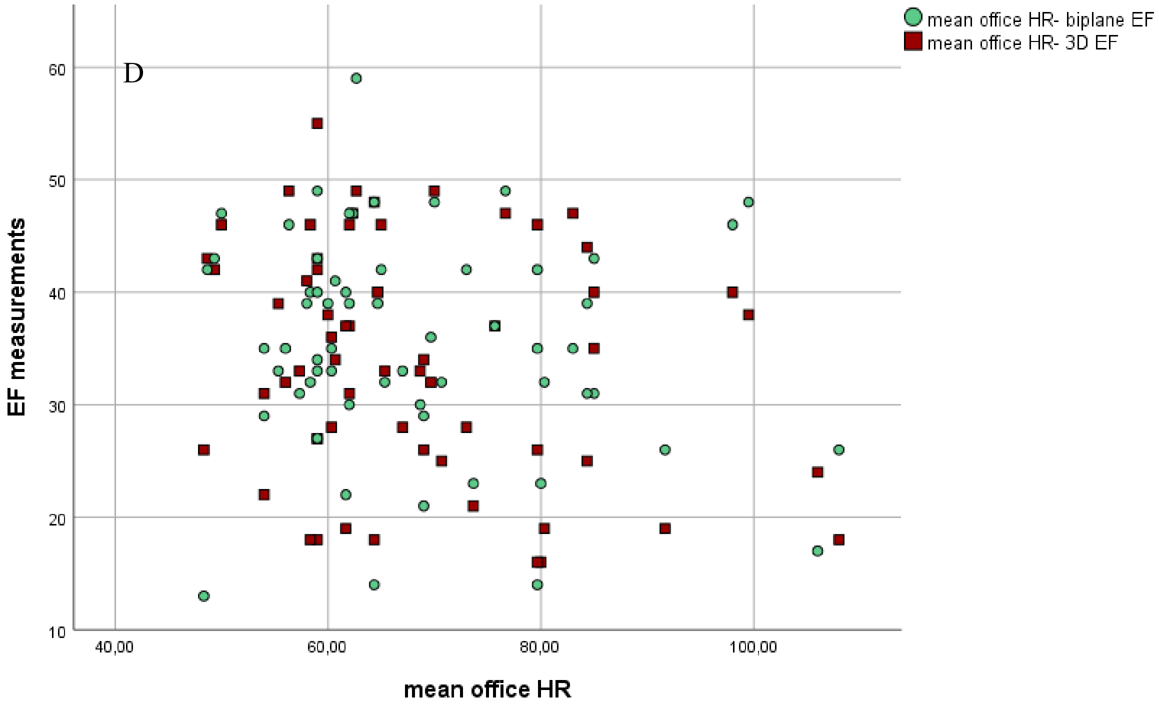
m24hnocHR



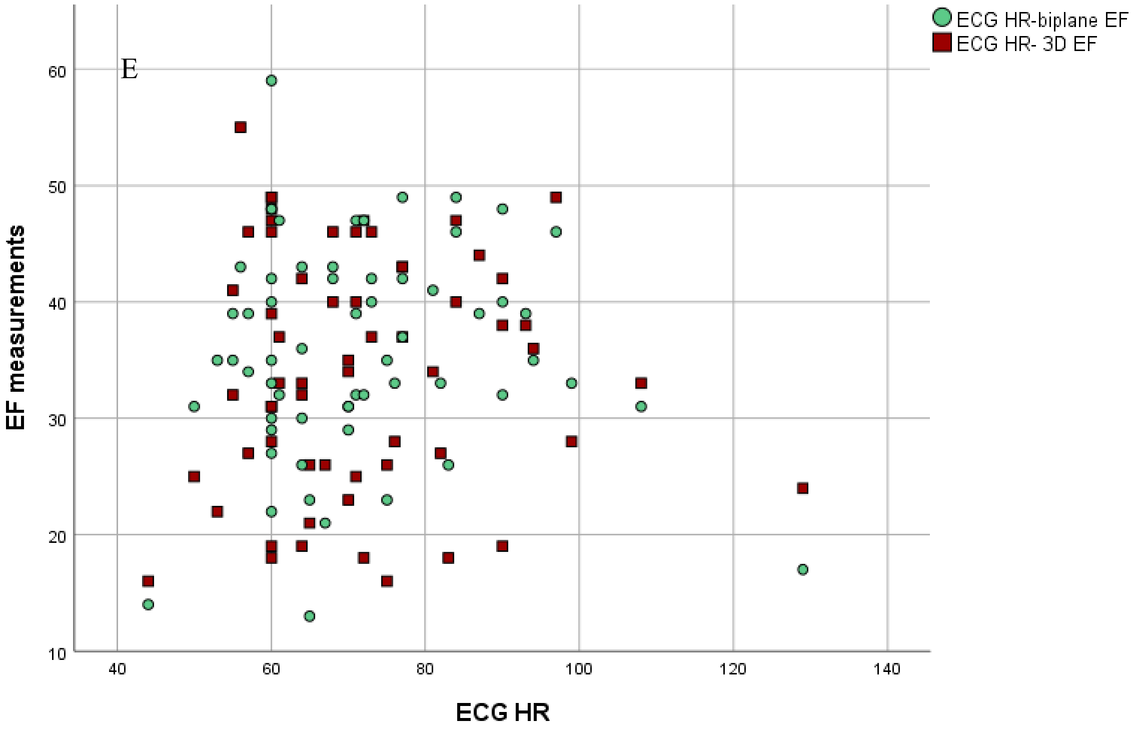


**Figure 24:** Correlation between different HR measurements and EF measurements

A) m24hHR measurements, for biplane EF p=0.905, for 3D EF p=0.503
B) m24hdayHR measurements, for biplane EF p=0.866, for 3D EF p=0.866
C) m24hnocHr measurements, for biplane EF p=0.549, for 3D EF p=0.549
D) office HR measurements, for biplane EF p=0.350, for 3D EF p=0.178
E) ECG HR measurements, for biplane EF p=0.424, for 3D EF p=0.818

### *EF in patients with sinus rhythm*

No measurement of heart rate correlated with the two different measurements of EF.

For the biplane EF it was: m24hHR (Pearson r=-0.094, p=0.510), m24hdayHR (Pearson r=0.017, p=0.903), m24hnocHR (Spearman r=0.099, p=0.480), officeHR (Spearman r=0.079, p=0.575) and ECG-HR (Spearman r=0.124, p=0.367).

For 3D EF measurements the following results were found: m24hHR (Pearson r=-0.041, p=0.818), m24hdayHR (Pearson r=0.009, p=0.959), m24hnocHR (Spearman r=0.099, p=0.590), officeHR (Spearman r=0.208, p=0.229) and ECG-HR (Spearman r=-0.094, p=0.580).

### *EF in patients with a stimulating pacing device*

No correlations to the different heart rate measurements were found in this subgroup.

For the biplane EF it was: m24hHR (Spearman r=-0.122, p=0.640), m24hdayHR (Spearman r=-0.235, p=0.363), m24hnocHR (Spearman r=-0.328, p=0.214) and officeHR (Spearman r=0.293, p=0.239) and ECG-HR (Spearman r=-0.047, p=0.852).

For 3D EF measurements the following results were found: m24hHR (Pearson r=-0.118, p=0.676), m24hdayHR (Pearson r=-0.159, p=0.572), m24hnocHR (Pearson r=-0.223, p=0.443), officeHR (Spearman r=0.104, p=0.703) and ECG-HR (Pearson r=-0.239, p=0.372).

### *EF in patients with atrial fibrillation*

And again, no correlations between the EF measurements and the heart rate measurements have been found.

For the biplane EF it was: m24hHR (Pearson r=0.045, p=0.803), m24hdayHR (Pearson r=-0.081, p=0.650), m24hnocHR (Pearson r=-0.087, p=0.630) and officeHR (Pearson r=-0.129, p=0.467) and ECG-HR (Spearman r=-0.131, p=0.466).

For 3D EF measurements the following results were found: m24hHR (Pearson r=-0.080, p=0.777), m24hdayHR (Pearson r=-0.171, p=0.525), m24hnocHR (Pearson r=-0.286, p=0.301), officeHR (Pearson r=0.042, p=0.878) and ECG-HR (Spearman r=-0.152, p=0.575).

# 4 Discussion

During this work, correlations between the different measurements of heart rate and other parameters were conducted. As NT-proBNP is such an important tool to determine the severity of heart rate, the correlations concerning this marker will also be discussed separately.

The results have shown, that all mean heart rate measurements correlated with each other, but the one single heart rate measurement (ECG heart rate) did not correlate with any other parameter. Statistical analysis has also shown no significant correlation between heart rate measurements and the ejection fraction.

As far as NT-proBNP is concerned, it correlated with the two different methods of measuring the ejection fraction. No correlations to heart rate measurements have been detected.

Detailed discussions of each evaluated factor can be found below; this will also include possible reasons of correlation, or the lack of it.

## 4.1 Impact of heart rate in heart failure patients

*Heart rate measurements*

It is commonly known, that achieving a lower heart rate (ideally <70 bpm) reduces the mortality in HFrEF patients, although this correlation is limited to HFrEF patients who present themselves with a sinus rhythm, in other cases, such as patients with a pacing device and those who present with AF, the correlation is yet unclear or insufficient. (34,38)

Heart rate is therefore seen as an important treatment target in HF, well covered by the SHIFT study, where the heart rate lowering agent was ivabradine (27).

According to current ESC guidelines, it’s recommended to include ivabradine in addition to the classic HF treatment, if the heart rate remains to be ≥70 bpm in symptomatic patients with a SR (6) .

During this study, quite a few patients presented themselves with a heart rate > 69.5 bpm and the ones having a sinus rhythm and exceeding this aspired heart rate, will now be mentioned: m24hdayHR measurement 22.3%, followed by ECG HR 20.4%, m24hHR 18.3%, mean office HR 15.5%, and m24hnocHR 14.4%.

Only two patients were found to receive ivabradine in addition to their normal treatment, one of them still exceeding the recommended heart rate and also showing at least one sign of arrhythmia. In this case, ivabradine was either not prescribed correctly or AF as a common side effect was observed. (39)
The other patient presented with a heart rate of 73 bpm during the m24hdayHR measurements, other measurements were within the norm.

It seems noteworthy, that the highest percentage of people with an elevated heart rate can be found in an ambulatory setting; a setting which best reflects their daily life, hence being a better prognostic marker. (40)

### *ECG heart rate*

The mean heart rate measurements itself correlated with each other but it was remarkably interesting to see that the ECG measurement did not seem to correlate with any of the measurements mentioned above. The mean heart rate in this subgroup was 71.9 ±15.9bpm, making it the highest mean heart rate measurement.

The following factors should illustrate the difference between the ECG heart rate measurement and the other heart rate measurements.

Firstly, the 12-lead ECG heart rate measurement is a single point measurement, whereas all the other heart rate measurements executed during this study where mean heart rate measurements. 58% of all study subjects have shown at least one sign of alternative pacing origin; this includes patients with AF and an implanted pacing device.
Previous studies have shown that short-term heart rate measurements in patients with AF were not useful for clinical consequences. (41,42)

Secondly, it was previously found that there is a significant difference between heart rate measurements at home and at the doctor’s office. This underlines the idea, that office heart rate measurements might not fully reflect the patient’s true heart rate (43).
For a correct heart rate measurement during a 12-lead ECG, an adequate resting period should be maintained and the measurement should be performed in a quiet room, both

factors were not always possible during this study, hence making the measurement fault-prone.

### *Heart rate and BMI*

Also, a significant correlation was found between the body mass index of the patients and all ambulatory heart rate measurements, as well as the mean office heart rate. The single heart rate measurement during the ECG did not correlate.

This would be especially worth looking at, as a ‘obesity paradox’ has been described, stating that overweight patients and mildly obese ones tend to have a better rate of survival when presenting with chronic HF (44).

There was no literature found if this phenomenon is annulled by the fact that there is an increased mortality when presenting with an elevated heart rate.

### *Heart rate and age*

An inverse correlation between age and m24hHR ($p=0.007$) as well as m24hdayHR ($p=0.021$) was found.

Previous studies support this correlation, as there is a decrease of the adrenergic system activity as people get older (45).

A possible explanation for the missing correlation between age and m24hnocHR ($p=0.073$) could be the increased prevalence of insomnia in elderly patients (46), making the nocturnal heart rate measurements not entirely representative for heart rate measurements during sleep. A survey covering insomnia was not included in this study.

## 4.2 Ejection fraction in heart failure patients

Measuring the left ventricular ejection fraction of HF patients is one of the most powerful tools to determine the severity of the illness and is also a crucial part of the recommended pharmacological treatment. (6)

During this study, two different measurements were included, the two-dimensional and the three-dimensional measurement.

They were found to correlate significantly ($p<0.001$) but it seems noteworthy that it was only possible to perform and evaluate 62 (63%) three-dimensional measurements of ejection fraction. The reason for this is manifold and includes the absence of a regular heartbeat, mainly due to AF, as well as poor imaging qualities, which includes the patient's inability to hold his or her breath. (47)

*Heart rate and ejection fraction*

No significant correlation was found between the ejection fraction of HFrEF patients and different heart rate measurements. It did not matter, whether a single point measurement, such as an ECG HR measurement was taken, or mean heart rate measurements.

The range of the measured EF was very small, with a limited variation. The highest EF in the biplane measurement was 55% and 59% in the 3D-measurement, whereas the lowest was 16% for the biplane measurement and 12% for the 3D-measurement. In contrast, the variation of heart rate was greater, making a correlation between those two parameters difficult.

Another factor, that should not be disregarded, is the medical treatment. 94% of all patients got a heart rate altering β-blocker, masking the 'true' inert heart rate and is therefore a bias in this particular correlation.

## 4.3 Limitation

Many patients seemed to have a good pharmacological HF treatment, making it rather difficult to assess the inert heart rate. There was no questionnaire being handed out, asking whether the HF treatment was taken correctly and/or regularly, hence posing an uncertainty during the evaluation.

The study patients were selected from HF patients, who routinely visited the department of cardiology of the Medical University of Graz. This preselection may come with a bias towards correct HF treatment in most patients.
No survey was conveyed on insomnia; hence the nocturnal heart rate measurement comes with another uncertainty of not knowing whether the patient was asleep or not.

During this study, patients were only seen once, and no follow-up was conducted. Therefore, no predictions can be made on the long-term effects of heart rate, EF, pharmacological treatment and other co-morbidities, which were investigated during the patient's visit.

# 5 Conclusion

As the highest percentage of elevated heart rate measurements was found in an ambulatory setting, further studies should be executed to evaluate the importance of ambulatory heart rate measurements for pharmacological treatment options.

Moreover, the lack of correlation between the ECG heart rate and the ambulatory heart rate measurements should be further investigated.

For statistically significant results, a greater study population ought to be considered for future studies concerning the relation between heart rate and EF measurements.
Until then, an elevation of heart rate and a lower EF should be seen as two independent risk factors in HF patients (48,49)

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