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Maastricht University

Faculty of Medicine and Life Sciences
School for Life Sciences
Master of Biomedical Sciences

Master's thesis

Taking heart failure patients out of the hospital: remote monitoring with wearable technology to enable outdoor cardiac rehabilitation

Charlotte Tuerlinckx

Thesis presented in fulfillment of the requirements for the degree of Master of Biomedical Sciences, specialization Clinical Molecular Sciences

SUPERVISOR :

Prof. Dr. Pieter VANDERVOORT

MENTOR :

Mevrouw Helene DE CANNIERE

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Acknowledgments

First of all, I would like to express my enthusiasm about the internship I have performed the last couple of months. It has been a true enrichment, both scientifically and personally. It has shown me a completely different side of biomedical sciences and made me realize that clinical research is where my interests are and where I want to develop myself. It was a beautiful ending of my 5-year student career at Hasselt University, which would not have been possible without Ziekenhuis Oost-Limburg, the Mobile Health Unit and Prof. dr. Pieter Vandervoort. Therefore, I would like to thank all of you.

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Abbreviations

6MWD	6-minute walk distance
6MWT	6-minute walk test
BB	ß-blocker
BMI	Body mass index
CIED	Cardiovascular implantable electronic device
CO	Cardiac output
CPET	Cardiopulmonary exercise test
CR	Cardiac rehabilitation
ECG	Electrocardiogram
FC	Functional capacity
FDA	Food and Drug Administration
HF	Heart failure
HR	Heart rate
HRR	Heart rate recovery
LV	Left ventricular
LVEF	Left ventricular ejection fraction
Max HR	Maximal heart rate
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NYHA	New York Heart Association
QoL	Quality of life
RHR	Resting heart rate
RV	Right ventricular
SF-36	Short Form 36 health survey
ZOL	Ziekenhuis Oost-Limburg

Abstract

Background - Heart failure (HF) patients suffer from exercise intolerance. Cardiac rehabilitation (CR) has been shown to significantly improve functional capacity (FC). However, current participation rates are low. Therefore, moving CR outside the hospital while monitoring progression using wearable technology, could play an important role in increasing enrollment of the typical HF patient. It is hypothesized that HF patients participating in CR can be evaluated in the same way outside the hospital as inside the hospital using a multiparametric wearable device.

Methods – For this preliminary study, twelve HF patients, participating in CR, were asked to perform a 6-minute walk test (6MWT) every three weeks, five times in total. Each test consisted of a 5-minute resting phase, followed by a 6MWT and a 5-minute recuperation phase. Patients were assigned to two groups and performed the 6MWT inside or outside the hospital accordingly. During the 6MWT patients were equipped with a multiparametric wearable device which measured ECG, bioimpedance and accelerometer signals.

Results - Total distance walked during the 6MWT increased throughout CR for both patients monitored inside and outside the hospital. However, resting heart rate (RHR) was lower and decreased more throughout rehabilitation in patients monitored outside the hospital. There was no difference in maximal heart rate (max HR) between both groups. However, the change in max HR throughout the CR program was different between groups. Max HR of patients monitored inside the hospital reached a plateau after the fourth test, while max HR of patients monitored outside continued to increase. Heart rate recovery (HRR) was significantly different between both groups at minute 4 and 5 after the 6MWT. Patients tested outside the hospital presented with a higher HRR compared to patients tested inside the hospital.

Discussion and Conclusion - Both groups improved throughout the CR program as shown by an increase in total distance walked, which indicates an increase in FC. However, ECG data collected by the wearable device demonstrated that FC cannot be assessed in the same way in HF patients that rehabilitate indoor and those who rehabilitate outdoor. Indeed, several HR parameters during the 6MWT were found to be significantly different in both groups. However, several limitations need to be taken into account. Nevertheless, it can be concluded that outdoor conditions affect performance in HF patients and that outdoor monitoring requires another way of interpretation.

1. Introduction

Heart failure (HF) is one of the most common causes of death in developed countries with a 5-year mortality rate of 50% (1). At present, more than 37.7 million individuals worldwide suffer from HF, covering approximately 2% of the adult population. Moreover, from the age of 45 the life time risk for developing HF ranges between 20% and 45%. As a consequence, up to 900 000 individuals are annually diagnosed with HF. Previous research shows that the prevalence of HF is expected to increase by 23% from 2012 to 2030. This is not surprising as HF is an age-dependent disease and the median age of the population continues to increase. In addition, improvements in pharmacological treatments and specialized care programs that raise survival rates among HF patients also contribute to the increasing prevalence (2). Hence, it is clear that HF is a major health problem that imposes a burden to society and the healthcare system. Unfortunately, current strategies to manage HF are insufficient to reduce this burden. Therefore, novel approaches that improve the quality of life of HF patients are urgently needed.

1.1. The pathophysiology of heart failure

HF is a complex clinical syndrome in which the cardiac output (CO) is insufficient to meet the metabolic requirements of the body. This is caused by a functional or structural abnormality of the heart which can result from a variety of causes including ischemic heart disease, hypertension and diabetes, as well as cardiomyopathies, infections, toxins, valvular disease and prolonged arrhythmias (1,3). As a consequence, HF can lead to several symptoms that substantially impact patients' daily life. These symptoms do not only restrict physical activities, but also limit social engagements and negatively affect emotional status, thereby reducing quality of life (QoL) (4).

HF can be classified into left ventricular (LV) and right ventricular (RV) failure. LV failure causes a decrease in CO and an increase in LV volume. These conditions may result in global hypoperfusion and pulmonary congestion, respectively, leading to symptoms such as fatigue and dyspnea (1). LV failure can be further divided into HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Patients with HFrEF have a reduced LV ejection fraction of $\leq$ 40% due to systolic dysfunction, i.e. impaired ventricular contraction and ejection. Patients with HFpEF have a normal LV ejection fraction of $\geq$ 55%, but suffer from diastolic dysfunction, i.e. impaired relaxation and ventricular filling (5). RV failure causes an

increase in RV volume, which in turn may lead to congestion of the liver, gastrointestinal tract and lower extremities. This results in symptoms such as nausea, lack of appetite, ascites and swelling of the legs, ankles or feet. In addition, RV failure also causes a decreased output from the right ventricle to the lungs, leading to dyspnea and fatigue (fig. 1) (1).

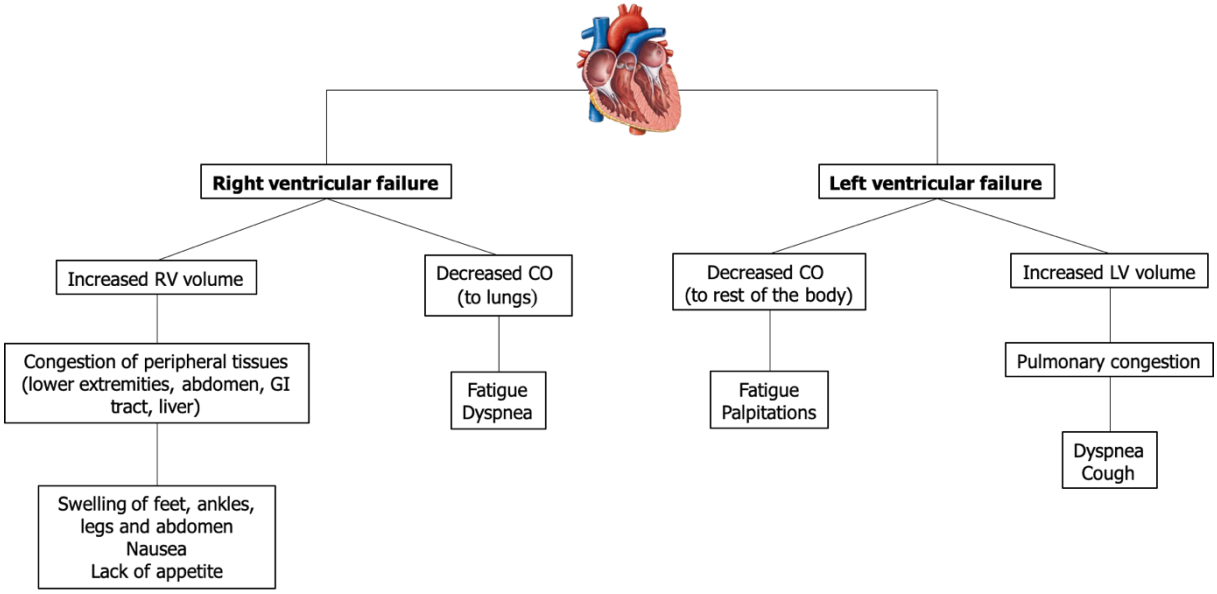

Figure 1. Schematic representation of RV failure versus LV failure.

1.2. Functional capacity

As the most common cause of RV failure is LV failure, patients with RV and LV failure often experience similar symptoms (1). Both LV and RV failure are characterized by fatigue and dyspnea, the hallmark symptoms of HF. These symptoms lead to a decreased functional capacity (FC), thereby causing exercise intolerance, which can be defined as the major disabling complication of HF. As such, fatigue and dyspnea are one of the most important factors that determine QoL in HF patients. Moreover, it has been shown that FC is a strong predictor of survival in patients with cardiopulmonary diseases (6). Therefore, assessment of FC is essential when evaluating the disease status of HF patients.

1.2.1. Cardiopulmonary exercise test

The gold standard to assess FC is the cardiopulmonary exercise test (CPET). This test measures several variables of gas exchange and cardiac function, including VO_2 max. VO_2 max is the maximum amount of O_2 the body is able to take up during exercise. It has been widely used as a marker for disease severity in patients with cardiopulmonary diseases, such as HF. In addition, it can also aid to diagnose HF early and to follow up progression of disease status in rehabilitation programs (7). Despite its accuracy in multiple applications, the CPET has some

major limitations. It requires sophisticated equipment, as well as the presence of experienced and qualified personnel. Moreover, it is very expensive and considered to be an invasive test for HF patients.

1.2.2. 6-Minute Walk Test

An alternative to the CPET is the 6-minute walk test (6MWT). This test measures the distance a patient can walk as fast as possible on a hard and flat surface within a time frame of 6 minutes. The total distance walked throughout the test is called the 6-minute walk distance (6MWD). In contrast to the CPET, the 6MWT assesses the *submaximal* FC during exercise (8). However, because the majority of daily activities do not have to be performed at maximal capacity, the 6MWT reflects the patient's tolerance to daily physical activities better than the CPET. In addition, the 6MWT has low requirements regarding personnel and equipment, is easy and fast to perform and is less invasive for the patients. Moreover, studies have shown that the 6MWD is correlated with VO_2 max as measured by the CPET (9–11). Therefore, 6MWT is considered to be a reliable and simple test to estimate FC in HF patients. Nevertheless, the 6MWT is patient-dependent and the 6MWD as a single outcome measure alone is not sufficient to give an accurate assessment of disease status. Additional parameters need to be taken into account allowing a proper interpretation of the outcome.

1.3. Cardiac Rehabilitation

Over the last decades, researchers have been focusing on cardiac rehabilitation (CR) to improve FC (12–17). CR can be defined as a long-term multidisciplinary intervention program that aims at improving the physical and emotional wellbeing of patients with a cardiovascular disease through educational and psychosocial support, as well as through exercise training (18). The benefits of CR have been well established. Especially exercise training has been shown to improve QoL by increasing FC and thereby reducing exercise intolerance (19,20). However, studies that investigate the effects of exercise training as part of a CR program on rehospitalization show conflicting results. While some of them show a significant reducing effect of CR on rehospitalization of HF patients, others are unable to reproduce these results (21–24). The main limiting factor in this story is non-adherence. Up to 60% of patients that are enrolled in CR indicate that they are not adherent to the prescribed exercise recommendations. Moreover, 33% to 56% of patients drop out during the exercise program. Barriers for participation and adherence to CR are extensive and are influenced by several factors, including ill-health, lack of motivation, transport or time. Therefore, long-term

outcomes of CR are rather poor (25). However, because study populations and rehabilitation programs of these studies appear to be very heterogeneous, it is difficult to compare the effects on rehospitalization.

1.4. Telerehabilitation and Remote Monitoring

One way to overcome these barriers is by moving CR outside the hospital. This can be realized by enabling telerehabilitation and remote monitoring of patients. Telerehabilitation does not restrict the patients to the hospital environment, but instead allows them to rehabilitate at any time and any place. As transport and time are major obstacles for attendance and adherence to CR, telerehabilitation may be an effective solution in making CR more accessible. Moreover, studies have shown that telerehabilitation is a feasible and effective alternative for the conventional in-hospital CR (26). However, to provide the same level of support and to be able to follow up their progression in FC, patients rehabilitating outside the hospital need to be monitored remotely. Remote monitoring includes the automatic transmission of clinical symptoms (fatigue, dyspnea, congestion) and/or physiological data (ECG, heart rate, blood pressure, weight) derived from an implantable or wearable monitoring device to a healthcare provider. This does not only allow physicians to control adherence and progression, but also allows them to anticipate adverse events and intervene before the patients become destabilized, thereby preventing hospitalization. Moreover, remote monitoring makes it possible for the physiotherapists to adjust the training workload from a distance without the need of a hospital visit (27).

1.5. Remote Monitoring Devices

Up to the present, only a limited number of devices have been proven clinically useful for remote monitoring of FC in HF patients. The majority of these devices are cardiovascular implantable electronic devices (CIEDs). In recent years, several studies showed that remote monitoring with a CIED positively affects patient outcomes and hospitalization number (28–30). However, others have shown that remote monitoring with CIEDs does not reduce rehospitalization or improve disease status (31–34). In addition, not every HF patient is qualified for a CIED and therefore remote monitoring through a CIED is only available for an exclusive group of HF patients. To enable effective remote monitoring for all HF patients, noninvasive techniques must be sought.

Various noninvasive remote monitoring devices and systems have been developed in recent years. One of the first systems to follow up health status of HF patients employed multiple monitoring devices, including a weighing scale, a blood pressure monitor and an ECG monitor, that each measured a specific parameter. Data collected by these devices was then transferred through a conventional telephone line to the central servers of the investigator site. This study showed that remote monitoring indeed may be an effective strategy to follow up health status of HF patients at home (35). However, the daily use of several devices can become a burden for the patient and therefore might limit the benefits of the system. Moreover, patient-collected data may not be reliable, as patients often do not have the same level of expertise as their caregivers. To overcome these problems, more user-friendly, automated and reliable alternatives have been investigated.

1.5.1. Noninvasive Remote Monitoring Devices

As the smartphone industry has been growing rapidly, it is not surprising that the potential of smartphone-based systems is being evaluated. The current FDA-approved smartphone monitor KardiaMobile (AliveCor®) consists of an electrode-embedded case that can be attached to a smartphone and captures an ECG signal from the user's fingertips after contact with the electrodes (fig. 2). The ECG can then be digitally viewed in real-time and is transmitted to the data server of the healthcare provider. Because of the widespread use of smartphones and the ease with which patients can monitor and transmit their ECG data to healthcare providers, these kind of devices offer a big opportunity for self-monitoring at home. However, mobile cardiac monitors do not provide continuous ECG monitoring (36,37).

Figure 2. Current noninvasive remote monitoring devices. (A) AliveCor® KardiaMobile monitoring device, (B) Carnation Ambulatory Monitor (CAM™, Bardy Dx®), (C) Zio-XT patch (iRhythm™).

In contrast, ECG patches such as Zio-XT (iRhythm™) and Carnation Ambulatory Monitor (CAM™, Bardy Dx®) are capable of continuous monitoring (fig. 3A/B). Generally, these patches consist

of a sensor system, an accelerometer, a processor and a battery, which are embedded in a relatively flexible material. Due to the adhesive properties of the material, the ECG patch can be easily affixed to the body (fig. 3C). Advantages of these devices are that they are easy to use, waterproof, wireless and minimally interrupting for daily activities. Unfortunately, they are for single use only and can be used for a maximum of a few weeks. Therefore their use is limited to ambulatory ECG monitoring (36,37).

1.5.2. Bioimpedance and Remote Monitoring

Although ECG monitoring devices such as KardiaMobile and Zio-XT are valuable tools for cardiac monitoring, they cannot provide sufficient warning for adverse events in HF patients (38). Anticipating adverse events requires the detection of congestion, as congestion is the most common reason for hospitalization of HF patients. Weight has been routinely used as a surrogate for congestion, but its clinical value remains uncertain (39). In a recent study of short-term medication omission in HF patients, no changes in body weight occurred although congestion increased. This indicates the low sensitivity of weight as a marker for congestion (40).

Studies indicate that bioimpedance might be a more accurate alternative to detect congestion (41–43). Bioimpedance can be defined as the resistance of biological tissues to electrical current. In transthoracic bioimpedance monitoring, source electrodes transmit an electrical current through the thorax. As this electrical current is conducted through tissues, detecting electrodes become aware of the tissue resistance and pursue the shortest and most conductive pathway. Since blood and other body fluids have a lower resistance to electrical currents than lung tissue, the electrical current passes through the thoracic fluid and the measured bioimpedance represents the fluid status of the thorax (44). This technique can also be used to monitor respiration parameters by measuring the movement of air throughout the lungs. Respirational parameters reflect congestion status in HF patients as it is often accompanied by shortness of breath. In addition, measuring respiration with bioimpedance does not require patients to sit still and can therefore be used during activities. It is during these activities that symptoms of HF become apparent, making the application highly desirable to measure disease status. Moreover, studies have shown that bioimpedance as a single indicator for congestion in HF patients lacks specificity and sensitivity (45–48). As HF is a complex clinical syndrome that cannot be comprised by a single parameter, detection of adverse events requires the measurement of additional parameters. Consequently, noninvasive monitoring devices that

are able of measuring several physiological parameters such as ECG, respiratory rate and activity simultaneously are promising alternatives for remote monitoring of FC in HF patients.

1.5.3. Noninvasive Multiparametric Monitoring Devices

Currently, there are only a few noninvasive devices that simultaneously measure multiple physiological parameters, including bioimpedance. Moreover, most of them are not suited for out-hospital measurements because they are difficult to operate and are not wearable, i.e they cannot be used while performing daily activities. Therefore, noninvasive *wearable* multiparametric monitoring devices are more interesting for use in telerehabilitation. A well-known example is the CoVa™ necklace (toSense™) (fig. 4). This multiparametric monitoring device consists of a wearable sensor that measures ECG and thoracic impedance, from which hemodynamic parameters and other vital signs can be calculated. The information measured by the necklace is send to a gateway (tablet or smartphone) which in turn forwards it to a web-based system that makes the information available for the physician (49).

Figure 4. CoVa™ necklace monitoring system.

This system is FDA-approved and has the ability to remotely monitor physiological parameters in HF patients which may aid in the identification, diagnosis and management of clinical conditions, events and trends. However, the clinical evidence of this device is rather scarce. Therefore, it remains uncertain whether it is qualified for the remote monitoring of HF patients. Moreover, in order to measure ECG and thoracic impedance with this device, patients need to be at rest for at least five minutes. As a consequence, the CoVa™ necklace cannot be used during activity, which is a major limitation.

1.5.4. A Novel Multiparametric Wearable Monitoring Device

Over the past decade, engineers of Holst Centre/imec Netherlands have been collaborating with physicians, clinical researchers and patients to develop a novel multiparametric wearable

monitoring device that is adapted to the needs and wishes of HF patients. This device is equipped with a bioimpedance sensor (BioZ), an ECG monitoring system and a 3-axis accelerometer, which are used to calculate HR, heart rate variability (HRV), respiration, thoracic fluid changes, activity level and posture. The multiparametric approach of the wearable allows for an improved follow-up of FC and disease status in HF patients. Moreover, because the wearable is a patient-tailored device, i.e. developed along with and for the patients, its design allows for continuous and long-term monitoring in a comfortable way.

At present, our research group aims at developing a score system by combining parameters that are measured by imec's wearable device. The idea behind this score system is that it supports caregivers and patients in assessing disease status in a more accurate and objective manner. The most commonly used classification system - the New York Heart Association (NYHA) system - is primarily based on subjective interpretations of symptom severity by physicians. Although it is widely used in clinical practice and is a useful predictor of mortality, it lacks validity and reproducibility (5). Therefore, there is a great need for an objective classification system. Measuring FC plays an important role in the development of such a classification system as it gives an objective estimation of a patient's disease status. Previous studies from our research group have already shown the potential of the wearable device to accurately measure parameters that are essential to assess disease status in HF patients (50,51). Therefore, it is a valuable tool for the development of the score system. Currently, it is also investigated whether the score system can be used to monitor FC in HF patients inside the hospital. Nevertheless, it is unknown whether the multiparametric wearable device is also capable of monitoring FC outside the hospital. Since telerehabilitation requires *remote* monitoring, it is of great importance to investigate the potential of the wearable device in an outdoor-setting.

1.6. Hypothesis and Research Objectives

This thesis will investigate the feasibility of a novel multiparametric wearable device to monitor FC and disease status in HF patients outside the hospital. The outcomes of this research could make CR more accessible, as rehabilitation can be moved outside the hospital if the wearable is capable of out-hospital monitoring. It is expected that this will lead to an increased number of patients participating in CR and therefore to a reduced number of rehospitalizations. Moreover, results of this project can aid in the further development of the score system mentioned previously. In the long run, this will allow for close monitoring of FC and disease status of HF patients at home. In this way, it will be possible to timely detect deterioration,

thereby preventing rehospitalization and optimizing the QoL of HF patients. In turn, the reduced rehospitalization number will lessen the economic burden that is associated with HF. The potential of the wearable device to monitor FC and disease status will be evaluated by means of the 6MWT. Regular follow-up of HF patients that participate in CR using the 6MWT inside and outside the hospital, allows us to determine whether the wearable device is able to monitor progression in an out-hospital setting.

It is hypothesized that HF patients participating in CR can be evaluated in the same way outside the hospital as inside the hospital during the 6MWT by using the novel multiparametric wearable device of imec. This hypothesis is supported by two objectives that evaluate the feasibility of the wearable device to monitor FC of HF patients during the 6MWT inside the hospital *(objective 1)* and outside the hospital, but in the hospital environment *(objective 2)*.

2. Methods

2.1. Study Population

From December 2018 until March 2019 the HiX patient database (ChipSoft, Amsterdam, The Netherlands) of Ziekenhuis Oost-Limburg (ZOL) was screened for patients that were eligible for enrollment in this feasibility study. A total of fifteen HF patients that recently started CR were voluntarily included in the study. The only inclusion criterium was a LVEF of less than 55%. Exclusion criteria were the inability to give informed consent, orthopedic or neurological limitations and limited language proficiency. Patients were subdivided into two groups. Group 1 was tested inside the hospital and group 2 outside the hospital, but within the hospital environment. All patients gave their written informed consent. The study complied with the Declaration of Helsinki and the study protocol was approved by the ethical committee of ZOL and Hasselt University (EC 14/085U).

2.2. Cardiac Rehabilitation

Patients that were eligible for this study had to be recently enrolled in the CR program. This program consists of 45 sessions of 1 hour and 15 minutes each, during which the patients perform several types of exercise. At the beginning of the rehabilitation program, each patient is asked to perform a CPET to estimate the FC. Based on these outcomes a personal exercise program is set up. This program comprises both endurance training, resistance training and high-intensity interval training. As the patients progress, the exercise program is re-evaluated and adjusted if necessary. It is recommended to attend the rehabilitation three times a week. Halfway the program and at the end, patients perform another CPET to estimate the progression of their FC.

2.3. Noninvasive Multiparametric Wearable Device

The novel multiparametric wearable device of imec (fig. 5) that was used for this study continuously collects ECG, bioimpedance and accelerometer data. The ECG signal was measured with a sampling frequency of 512 Hz by three electrodes: left (L), right (R) and bias (B) (fig. X). The left and right electrode represented lead II of Einthoven's triangle. As lead II was positioned according to the cardiac depolarization direction, it generated the most accurate QRS complex. In addition, the bias electrode, which was positioned in the center of the upper body underneath the thorax, improved signal quality by reducing the noise that was caused by movement. This facilitated peak detection during data processing.

Bioimpedance was measured by four electrodes at a fixed single frequency of 80 kHz with a sampling frequency of 1024 Hz (fig. 5). A tetrapolar configuration was chosen to diminish the effect of skin-electrode impedance. In the configuration that was used for this study two source (S) electrodes were positioned at each side of the thorax on the midaxillary line at the level of the intercostal line and transmitted an electrical current. This current was measured by two detecting (D) voltage electrodes that were also positioned at each side of the thorax on the midaxillary line at the level of the intercostal line. This electrode configuration was selected based on a previous study that investigated which electrode configuration generates the most optimal bioimpedance signal quality. Two configurations appeared to be eligible, but preference went out to the configuration described above because it is more comfortable for the user and easier to apply in female patients (52).

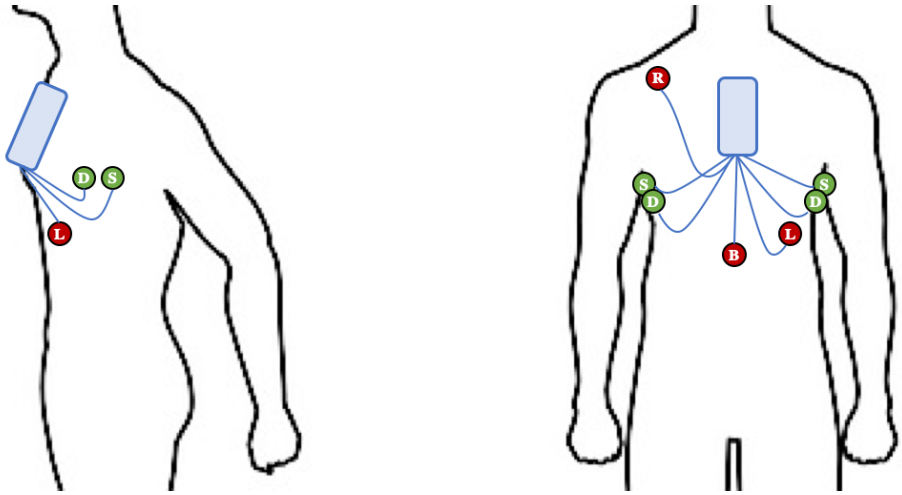

Figure 5. Positioning and configuration of the multiparametric wearable device.
(R) right, (L) left, (B) bias, (S) source electrode, (D) detecting electrode.

The accelerometer signal was measured by a 3-axis accelerometer module with a sampling frequency of 32 Hz. The wearable device itself was positioned on the upper part of the thorax (fig. 5). All measurements were stored in text files (.txt) on a micro SD card and transferred to a computer via a USB connection.

2.4. Experimental protocols

All patients performed a 6MWT every three weeks, five times in total. Prior to the test, patients were equipped with the wearable device (fig. 5). According to the group to which the patients belonged, they performed the test inside or outside the hospital. After the first and last test, patients were asked to fill in two questionnaires regarding their heart disease.

2.4.1. 6MWT

Before the onset of the 6MWT patients were set at rest in a wheelchair for at least five minutes. During this period, blood pressure was measured, general health status was evaluated and the appropriate NYHA class (Sup. table 1) was assigned. Immediately before the beginning of the test, HR and oxygen saturation were measured using a pulse oximeter. Additionally, baseline dyspnea and fatigue were estimated using the Borg scale (Sup. table 2).

Once the patients were positioned at the starting point of the track, they were asked to take a deep breath before starting their walk. During the six minutes of the test, the number and duration of laps were measured. In between the laps, standardized encouragements were repeated. After six minutes patients were asked to stop and were set at rest in a wheelchair to recuperate for five minutes. During the recuperation phase HR, oxygen saturation and blood pressure were measured. Post-walk dyspnea and fatigue were assessed using the Borg scale. The number of laps, as well as the additional distance were documented and the total distance walked was calculated.

The 6MWT inside the hospital was performed on a hard, flat and smooth surface in an enclosed corridor. Outside testing was performed on a concrete, flat surface in the neighborhood of the hospital. Both the indoor and outdoor walking track measured 45 meters in length and were marked every five meters. Patients were informed that the objective was to walk as far and fast as possible in six minutes. Nevertheless, they were allowed to perform the test at their own exercise intensity. Whenever they deemed it necessary, they could slow down, stop and rest. However, the timer kept running. As soon as they were able to walk again, they had to resume the test. Patients were not permitted to talk during the walking test as this could interfere with the quality of ECG and bioimpedance measurements.

2.4.2. Questionnaires

After the first and last 6MWT, patients were asked to fill in the Short Form 36 Health Survey (SF-36) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) to gather information about their health status and the adverse effects of HF on their lives. The SF-36 Healthy Survey is a multi-purpose questionnaire which consists of 36 questions that cover eight health concepts: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to personal or emotional problems, and mental health. Each health concept is scored on a scale of 0 to 100,

with higher scores indicating less disability and more wellbeing. The MLHFQ is a disease-specific questionnaire that assesses the physical and emotional impact of HF on the daily lives of HF patients during the preceding month, thereby assessing their QoL. This questionnaire measures 21 HF-related items on a 6-point Likert scale (0 = no, 5 = very much) that may adversely affect daily life. It is scored by summation of all item responses, with higher scores representing poorer QoL.

2.5. Data processing

Raw data collected by the wearable device was processed in MATLAB® (The MathWorks Inc., Natick, MA, USA) using specialized algorithms that were developed by imec. First, raw signals encrypted in *.txt* files were converted to interpretable comma separated value (*.csv*) files. These *.csv* files were fragmented into three parts: resting phase, walk phase (6MWT) and recuperation phase. After segmentation, ECG signals were filtered to eliminate noise and ensure high-quality data to improve R-peak detection. Next, the filtered parts were processed to create a resting phase that started exactly 5 minutes before the onset of the 6MWT, a walk phase of exactly 6 minutes and a recuperation phase of 5 minutes that immediately followed the 6MWT. In this way signals were created that could be compared between different patients. The new ECG signals were used for the detection and manual inspection of R-peaks. Based on this R-peak detection a series of variables was created, including RR-interval, HR and HRV. Bioimpedance signals have not been used for the analysis and therefore were not further processed after segmentation.

2.6. Statistical analysis

Statistical analyses were performed using SPSS Statistics. Continuous variables are expressed as mean $\pm$ standard deviation if normally distributed or as median (interquartile range) if non-normally distributed and categorical data are expressed as n(%). Normality was assessed using the Shapiro-Wilk test. Continuous variables were compared between both groups using independent-samples t-test and Mann-Whitney U test. Categorical variables were compared using Fisher's exact test and Chi-square test. To assess intra-individual progression over time, repeated measures ANOVA and Friedman test were used. Correlations between two continuous variables were calculated with Pearson's correlation and Spearman's correlation.

3. Results and Discussion

3.1. Study Population

From December 2018 to March 2019, 129 cardiac patients were included in the CR program and assessed for eligibility. Sixteen patients met inclusion criteria. One patient was not interested and fifteen patients agreed to participate. Eight patients were assigned to group 1 and seven patients to group 2. One patient was excluded due to orthopedic limitations that presented during the study and two patients dropped out due to ill health. One patient only completed three 6MWTs, but was still included in the data analysis. In total twelve patients were included in the data analysis, six in each group (fig. 6).

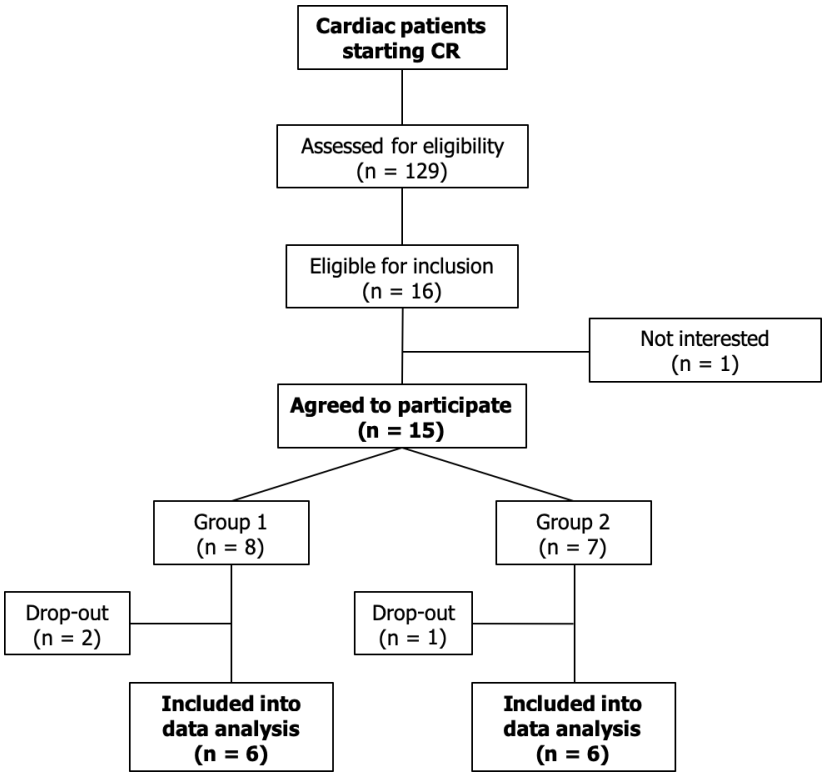

Figure 6. Flowchart of study population.

Baseline characteristics of the patient population are shown in table 1. The patient population consisted of nine male (75%) and three female (25%) subjects, with a mean age of 62 ± 13 years and a mean BMI of 25.9 ± 2.6. Patients had a mean LVEF of 41.6 %, with most of them reporting symptoms of NYHA functional class I (25%) or II (50%). Patients of this HF population were younger, less likely female and presented with a higher LVEF compared to a general HF population. In addition, this patient population mostly reported symptoms of NYHA class I and II, rather than symptoms of NYHA class III and IV as in a general HF population. Moreover, these study patients presented with less comorbidities than in general (53).

However, the majority of baseline characteristics of this HF population do resemble those of other HF patients participating in cardiac rehabilitation or undergoing exercise training (12,13). Indeed, HF patients that are too ill to exercise tend to reject participation in CR, while older HF patients often are not able to attend CR due to a lack of transport. As a consequence, HF patients that attend CR are generally younger and in better health.

Table 1. Baseline characteristics of total population, group 1 and group 2.

Variable	Total	Group 1	Group 2	p
Male	9 (75%)	4 (66.7%)	5 (83.3%)	1.000
Age	62 ± 13	59 ± 7	66 ± 16	0.373
Height (cm)	172.2 ± 7	171.3 ± 5	173.0 ± 8.9	0.699
Weight (kg)	77.1 ± 10.2	77.1 ± 9.8	77.1 ± 11.5	0.996
BMI	25.9 ± 2.6	26.3 ± 3.5	25.6 ± 1.4	0.674
BSA	1.90 ± 0.15	1.89 ± 0.11	1.91 ± 0.19	0.865
Baseline disease status				
LVEF (%)	41.6 ± 7.6	38.6 ± 7.4	44.6 ± 7.1	0.183
NYHA class				
• Class I	3 (25%)	1 (16.7%)	2 (33.3%)	0.740
• Class II	6 (50%)	4 (66.7%)	2 (33.3%)	
• Class III	2 (16.7%)	1 (16.7%)	1 (16.7%)	
• Class IIII	1 (8.3%)	0 (0%)	1 (16.7%)	
Medication				
ACE-inhibitor	17 (94.4%)	5 (83.3%)	6 (100%)	1.000
BB	16 (88.9%)	4 (66.7%)	6 (100%)	0.455
Diuretic	12 (66.7%)	3 (50%)	3 (50%)	1.000
Comorbidities				
Diabetes	1 (8.3%)	0 (0%)	1 (16.7%)	1.000
Hypercholesterolemia	5 (41.7%)	2 (33.3%)	3 (50%)	1.000
Hypertension	4 (33.3%)	2 (33.3%)	2 (33.3%)	1.000
Smoking status				
• Never smoked	6 (50%)	3 (50%)	3 (50%)	1.000
• Ex-smoker	3(25%)	1 (16.7%)	2 (33.3%)	
• Smoker	3 (25%)	2 (33.3%)	1 (16.7%)	

There was no statistically significant difference in clinical characteristics between patients of group 1 and group 2. However, mean LVEF was considerably higher in patients of group 2,

which indicates that it is likely that these patients are healthier. Moreover, mean age was also lower in group 1 compared to group 2. As patient groups are small, it is important to take into account these differences since they can significantly affect outcomes.

3.2. Outcomes of CPET

All patients performed a CPET at the start of the CR program to estimate their baseline FC and a second one halfway through the program to assess their progression. There was no difference in baseline VO_2 max between group 1 and 2 ($p = 0.998$), nor was there a difference halfway the CR program ($p = 0.662$, table 2).

Table 2. Difference in VO_2 max between group 1 and 2.

	Group 1	Group 2	p-value
VO_2 max baseline	17.2 ± 1.7	17.2 ± 6.2	0.998
VO_2 max between	19.9 ± 1.8	18.6 ± 5.0	0.662

Few weeks after initiating CR, patients of group 1 did not show a significantly improved VO_2 max ($p = 0.104$). However, an increasing trend was observed. In patients of group 2, VO_2 max showed a significant increase ($p = 0.050$). In the past, several studies already revealed that VO_2 max considerably increases after CR. (54). Therefore, findings of this study are in accordance with previous research. Nevertheless, the results are not statistically significant, but they indicate a trend. The reason for this is that some patients performed another test to estimate their FC and no VO_2 max was recorded during this test. As a consequence, only four patients of group 1 and four patients of group 2 were included into the statistical analysis. In addition, CPET does not always give a good representation of the actual disease status as HF patients may experience day to day fluctuations in symptoms, which can negatively affect the outcome of the CPET. Therefore, these findings indicate once again that the 6MWT should be preferred over the CPET to estimate FC in HF patients (10,11).

In addition, a linear relationship was found between VO_2 max and 6MWD (Sup. fig. 1). Analysis showed that 6MWD was significantly and strongly correlated with VO_2 max ($r = 0.768$, $p < 0.0001$). This confirms that the 6MWT is a reliable alternative for the gold standard CPET and can be used to assess functional progression, which has also been demonstrated by others (10,11,59).

3.3. Outcomes of 6MWT

At baseline, total distance walked during the 6MWT ranged between 321 and 715 meters with a mean of 529 ± 112 meters. During the final 6MWT, total distance walked ranged between 494 and 795 meters with a mean of 647 ± 84 meters. There was no significant difference in total distance between group 1 and 2 during the first 6MWT, nor was there a difference during the following 6MWTs (table 3).

Table 3. Difference in 6MWD between group 1 and 2 per measurement.

6MWD is expressed in meters.

	Group 1	Group 2	p-value
6MWD 1	529 ± 97	529 ± 135	0.992
6MWD 2	593 ± 60	576 ± 128	0.785
6MWD 3	625 ± 51	611 ± 118	0.791
6MWD 4	637 ± 43	626 ± 139	0.874
6MWD 5	642 ± 35	653 ± 126	0.863

After twelve weeks of rehabilitation, both groups showed a significantly improved 6MWD ($p_1 = 0.006$, $p_2 < 0.0001$) (fig. 7). Patients of group 1 and 2 improved their 6MWD with an average of 24.9% and 23.2%, respectively, compared to baseline.

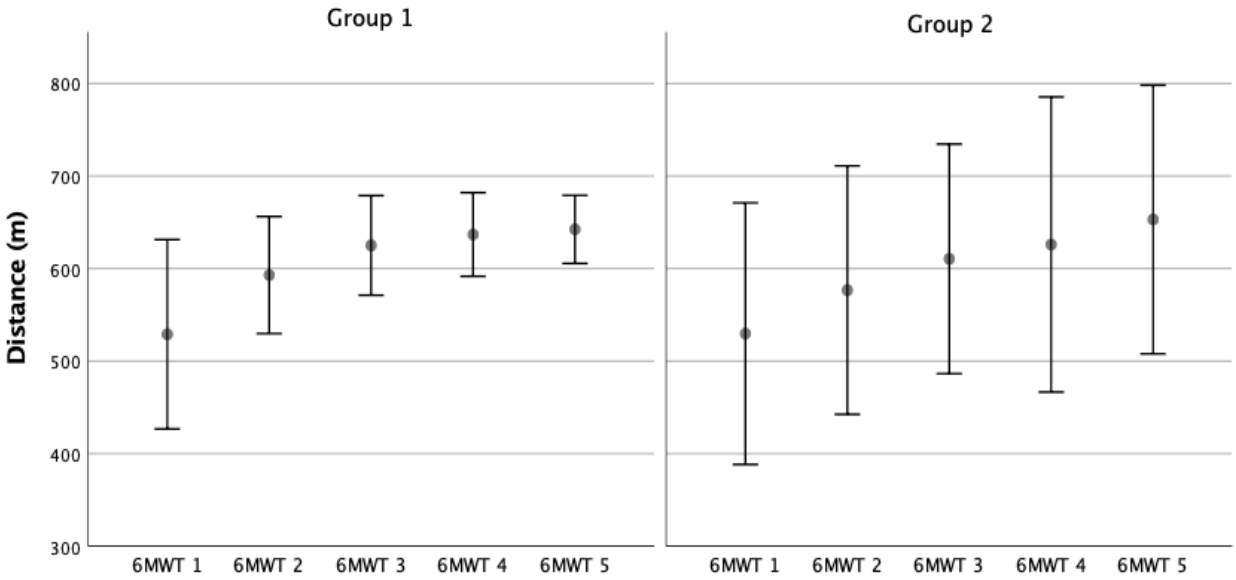

Figure 7. Overview of mean 6MWD of group 1 and 2 per test.

There was no practice test provided in this study. The first 6MWD was used as baseline measure. However, some researchers have recommended to perform a practice test in order to accurately define the effect of rehabilitation on the 6MWD (55–57). In contrast, other

studies have shown that a practice test is unnecessary in most clinical settings, as the 6MWD is only slightly higher during a second 6MWT, performed one day later (8). Moreover, patients still improved significantly when the second 6MWD was taken as baseline measure ($p_1 = 0.010$, $p_2 = 0.001$).

Furthermore, a similar trend in progression was seen in group 1 and 2. Patients improved most between the first and second measurement and then gradually improved less until they reached their maximum capacity (fig. 8). In group 2, patients seemed to have deteriorated during the fourth test compared to the third and then improved again during the last test. However, one of these patients experienced an abnormally high number of extrasystoles during the fourth test and stopped walking due to dyspnea. As a consequence, this patient's 6MWD was lower than before. During the fifth test, the patient did not experience any similar symptoms and was able to walk more. Since group sizes are small, this outlier considerably affected the results.

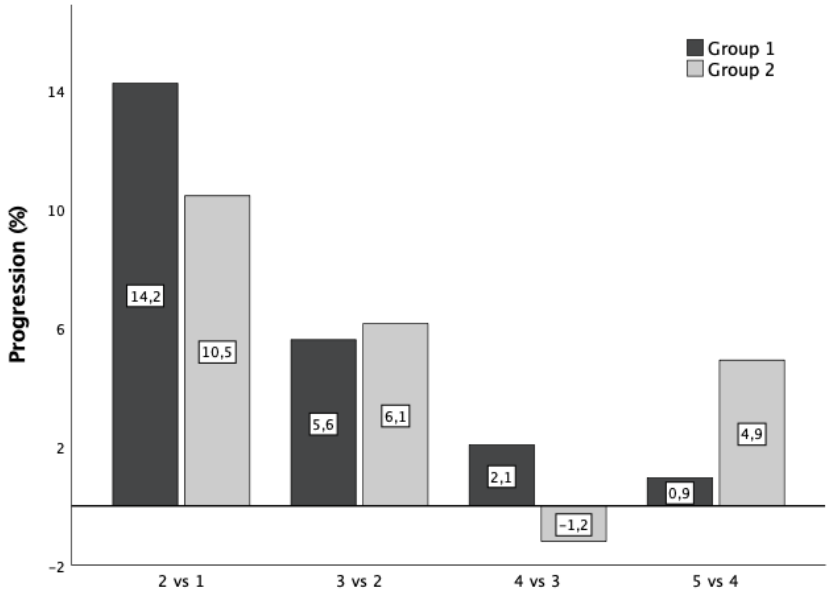

Figure 8. Progression in 6MWD compared to previous test expressed in percentages.

It was also noticed that patients with a low baseline distance (< 350 m) improved more compared to other patients ($p = 0.036$), independent of the group to which they belonged. Patients that walked less than 350 meters during the first 6MWT improved their 6MWD with a mean of 63.15%, while patients with a higher baseline distance increased their 6MWD with a mean of 15.5%. These findings agree with previous research and show once again that patients with the lowest FC benefit the most from a CR program (58).

3.4. Outcomes of Multiparametric Wearable Device

3.4.1. Resting Heart Rate

Resting heart rate (RHR) for each measurement is shown in table 4. At baseline, RHR ranged between 45 and 103 bpm with a mean of 74 ± 17 bpm. During the final test, RHR ranged between 44 and 94 bpm with a mean of 70 ± 15 bpm. From the second 6MWT, RHR was found to be significantly lower in group 2 compared to group 1. This can be attributed to the fact patients of group 2 appeared to be healthier than patients of group 1, as previously shown. Especially LVEF was higher in group 2 compared to group 1 (44.6% vs 38.6%). As LVEF is a valuable measure for estimating disease status, patients of group 2 presumably were in better health and therefore presented with a lower RHR.

Table 4. Difference in RHR between group 1 and 2 per measurement.

RHR is expressed in bpm.

	Group 1	Group 2	p-value
RHR 1	79 ± 10	69 ± 21	0.325
RHR 2	80 ± 5	61 ± 15	0.025
RHR 3	79 ± 2	58 ± 12	0.006
RHR 4	78 ± 7	59 ± 13	0.013
RHR 5	80 ± 10	58 ± 10	0.006

In addition, a moderate negative correlation was found between RHR and 6MWD in group 2 (r_S = -0.694, $p < 0.0001$), but not in group 1 (r_S = 0.145, $p = 0.452$). This suggests that RHR does not define progression in FC in patients of group 1. It was previously shown that both groups improved their FC, since 6MWD increased throughout the CR program. In patients of group 2 this improvement was associated with a reduction in RHR, while in patients of group 1 RHR and 6MWD did not simultaneously improve. However, in both groups RHR did not significantly decrease throughout the CR program ($p_1 = 0.949$, $p_2 = 0.168$). In patients of group 1, mean RHR remained stable and did not fluctuate. Based on RHR only, one would say that group 1 did not improve throughout the CR program, while the increase in 6MWD indicates the opposite. This shows once again that multiple parameters have to be taken into account to determine whether patients are improving. In contrast, in group 2 mean RHR reduced by 9.8% on average. Nevertheless, no significant difference was seen, despite the fact that previously reported data shows that exercise training reduces RHR both in healthy individuals and cardiac patients (60,61). However, Huang et al. demonstrated that in older adults this effect might only become apparent after at least 30 weeks of training (62). Patients included

in this study follow a CR program of 15 weeks and therefore might not benefit a reduction in RHR. In addition, HR is a highly variable parameter and normal values of RHR can vary widely from person to person. It can be influenced by several factors and does not solely depend on disease status. In some patients HR automatically increases upon seeing a physician or undergoing an examination. Since both patient groups consist of only six patients, this effect can be very prominent and can give a wrong representation of reality.

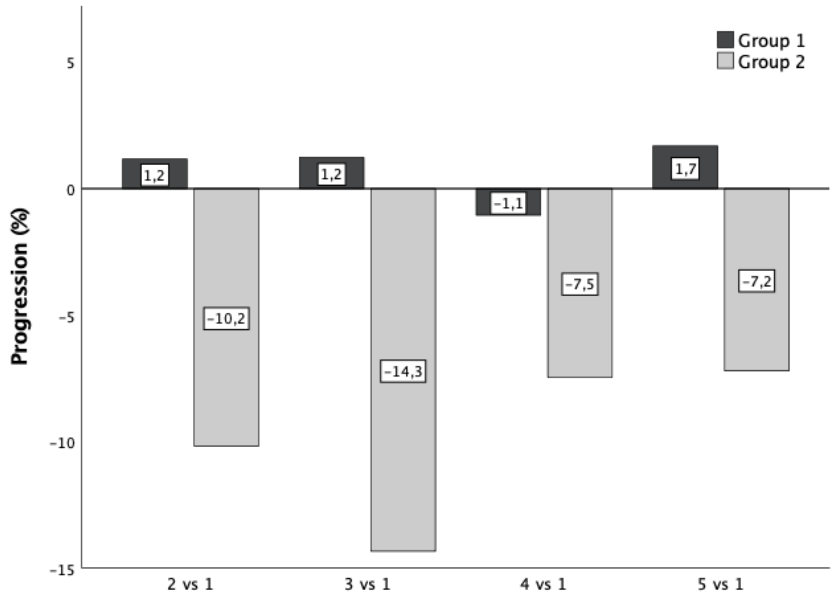

Figure 9. Progression in RHR compared to baseline measurement expressed in percentages.

This also became clear in the fourth measurement of group 2 when RHR increased again while no changes in medication or health status were reported (fig. 9). One of the patients presented with an abnormally high number of extrasystoles during the fourth test. As a consequence, more R peaks were detected and HR increased. During any other measurement, both before and after this test, the patient did not experience something similar and HR was lower. This demonstrates again that HR is strongly person-dependent and may change from day to day. Therefore, these findings emphasize the importance of a personalized approach in the treatment of HF.

3.4.2. Maximal Heart Rate

Maximal heart rate (max HR) for each measurement is shown in table 5. At baseline, max HR ranged between 69 and 135 bpm with a mean of 107 $\pm$ 19 bpm. After twelve weeks of rehabilitation, max HR ranged between 68 and 143 bpm with a mean of 115 $\pm$ 18 bpm. There was no difference between group 1 and 2 during the first 6MWT, nor were there differences between group 1 and 2 during the other measurements.

Table 5. Difference in max HR between group 1 and 2 per measurement.

Max HR is expressed in bpm.

	Group 1	Group 2	p-value
Max HR 1	107 ± 16	108 ± 23	0.896
Max HR 2	110 ± 5	111 ± 25	0.924
Max HR 3	119 ± 11	114 ± 26	0.669
Max HR 4	120 ± 12	117 ± 26	0.800
Max HR 5	124 ± 13	119 ± 15	0.607

In patients of group 1 a significant difference was found between baseline and final max HR (*p = 0.020*). In contrast, in group 2 no considerably significant difference was seen (*p = 0.084*), despite the fact that research has shown that long-term physical training improves max HR in cardiac patients (63). However, a number of values was missing for some patients, because walking caused noise on the ECG signal and made R peak detection difficult or not possible, since no appropriate algorithm has been developed yet to detect R peaks during exercise. As a result, not all patients were included into the data analysis. Nevertheless, the change in max HR before and after a physical training program in a recent study of Ehlken et al. was similar to the change in these patient groups (64). In their intervention group max HR improved with 12.8%, in contrast to 12.7% in group 1 and 16.6% in group 2 of this study. This suggests that the patient population is too small to demonstrate a significant difference. Still, the low p value of group 2 indicates a trend toward significance.

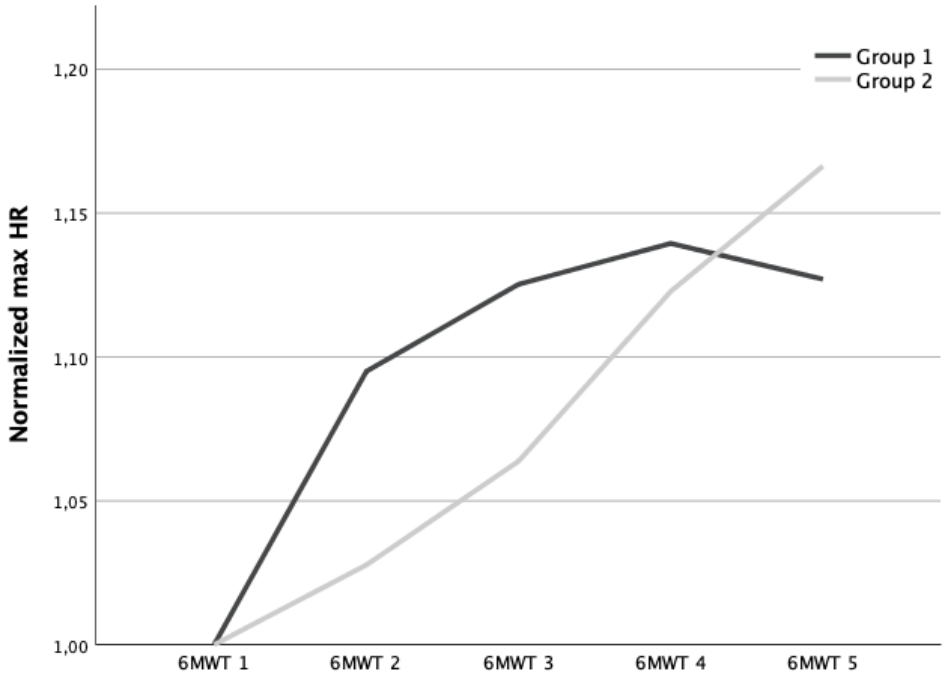

Figure 10. Difference in progression of normalized max HR between group 1 and 2.

However, group 1 and 2 did not improve similarly, but presented with a different trend (fig. 10). Patients of group 1 improved their max HR most between the first and second 6MWT (9.5%). During the subsequent tests, max HR continued increasing, but reached a plateau by the fourth test. In patients of group 2 max HR improved most between the third and the fourth 6MWT (5.7%). In contrast to group 1, max HR in group 2 did not reach a plateau by the fourth test, but continued increasing. This would suggest that patients from group 2 benefit more from a CR program and that their improvement is related to regularly performing a 6MWT outdoor. However, it is very unlikely that the performance of a 6MWT every three weeks can affect a patient's outcome in such a way. A more plausible explanation would be that there were differences between group 1 and 2 that influenced the results. For example, in group 1 half of patients indicated that their legs felt heavy during the 6MWT and that it stopped them from walking faster, although they did not experience dyspnea. Because they were not able to walk faster, their HR could not increase as much as other subjects not experiencing this symptom. In contrast, in group 2 only one patient indicated to have this feeling of heavy legs. As a result, max HR increased more in group 2 than in group 1. Outcomes of the Borg scale do not confirm this finding as no significant difference was found in fatigue and dyspnea between group 1 and 2 during any of the measurements. However, the Borg scale is a subjective tool and patients do not always correctly estimate the intensity of their fatigue and dyspnea. Some patients do not want to admit that they feel exhausted because they have difficulty with accepting that they are not as healthy as someone else. Other patients have become used to feeling exhausted and therefore underestimate their symptoms. Another factor that could have caused a difference between both groups is that in group 2 two subjects presented with an exceptionally high HR during the fourth and fifth 6MWT, respectively. Since group sizes are very small, this might have considerably affected mean max HR and caused it to continue increasing instead of becoming stable.

The fact that patients of group 1 reached a plateau suggests that they no longer benefit from the CR program from this moment. It would be interesting to consider whether their CR program can be changed to prevent this from happening or, in case this would not work, to stop their rehabilitation earlier. However, it has not been studied before how max HR evolves during a CR program and therefore it is difficult to define what can be considered as normal or expected. When analyzing patients individually, it becomes clear that max HR does not consequently increase throughout a CR program, but presents with ups and downs (fig. 11). This illustrates the day to day fluctuations in symptoms that patients with HF experience and how it affects daily life. Moreover, it demonstrates the wide variety within the HF population

and that HF patients do not benefit equally from a CR program. These findings highlight once again the need for personalized approaches to HF.

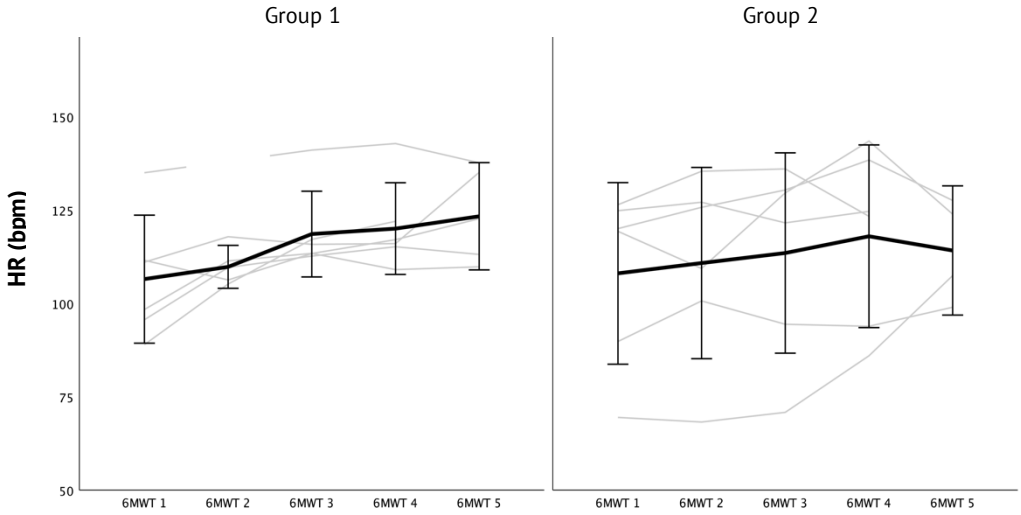

Figure 11. Individual and mean progression of max HR per group expressed in bpm.

3.4.3. Maximal Heart Rate and 6MWD

No correlation was found between max HR and 6MWD. In contrast, normalized max HR and normalized 6MWD were significantly positively correlated (r_s = 0.625, *p<0.0001*). This indicates that the change in max HR increases as the change in 6MWD increases. However, the correlation between normalized max HR and normalized 6MWD was stronger in group 1 (r_s = 0.792, *p <0.0001*) than in group 2 (r_s = 0.447, *p = 0.017*) (fig. 12). These findings suggest that HR and distance are more dependent on each other in an indoor setting. Moreover, they suggest that an outdoor environment may affect max HR independent of the distance.

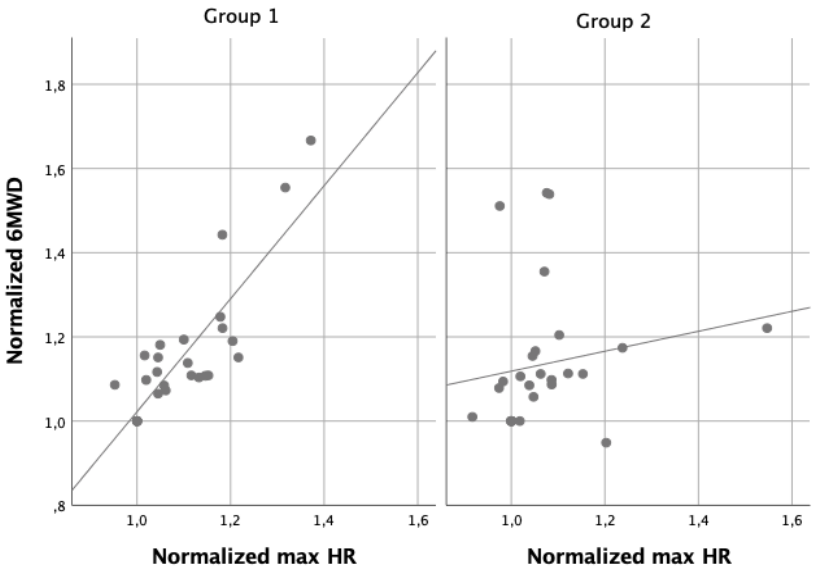

Figure 12. Correlation between normalized max HR and normalized 6MWD per group.

Nevertheless, these results indicate that max HR is an important parameter in both indoor and outdoor testing that must be taken into account when evaluating patients' progression throughout the rehabilitation program.

3.4.4. Heart Rate Recovery

Heart rate recovery (HRR) was not significantly different between group 1 and 2 at minute 1, 2 and 3 after the 6MWT during each measurement. However, at minute 4 and 5 after the 6MWT HRR was considerably higher in group 2 (fig. 13). The difference between group 1 and 2 at minute 4 and 5 was significant or showed a tendency toward significance during nearly every measurement (Sup. table 3). Only during the third measurement no significant difference was seen at minute 4 and 5 and during the fifth measurement no difference was seen at minute 5. Nevertheless, p values were also low during these measurements and therefore indicate a positive trend as well.

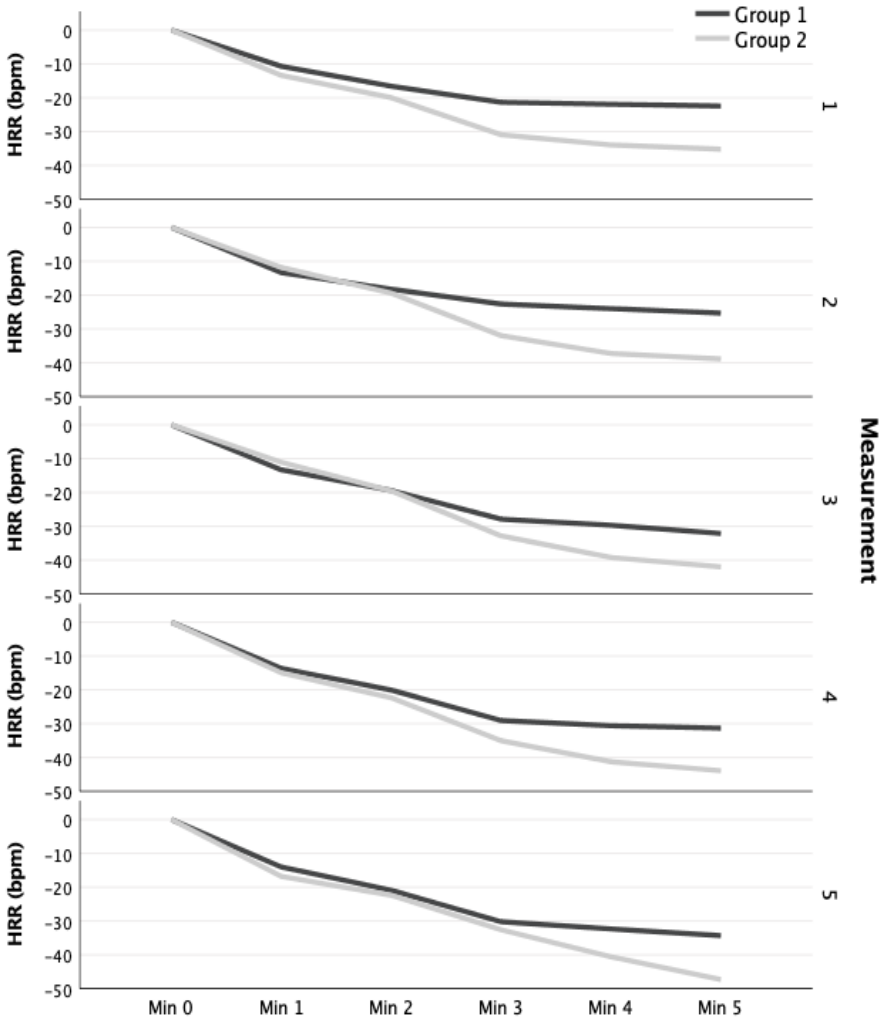

Figure 13. Difference in HRR between group 1 and 2 per measurement.

HRR is expressed in bpm.

The difference between both groups concerning HRR is the result of a greater heart rate reserve in group 2 compared to group 1. As previously shown, both RHR and max HR improved more in patients of group 2. Because RHR was lower in these patients compared to patients of group 1, it is obvious that HRR is greater as well. However, it is doubtful whether this is entirely due to the outdoor environment. Several years ago, Imai et al. demonstrated that HRR after exercise is increased in trained subjects, but blunted in HF patients. Both the sympathetic and parasympathetic nervous system play an important role in this effect. The initial decline in HR after exercise is predominantly affected by parasympathetic reactivation, whereas HRR at >2 minutes after exercise is mediated by sympathetic withdrawal (65). However, it is generally known that sympathetic activity is increased in HF patients, but parasympathetic activity reduced. Therefore, HF patients show a decreased HRR. These findings suggest that sympathetic activity is already lower in patients of group 2 from the beginning of the CR program. The question remains whether this is due to the outdoor setting or due to the fitness level of the patients. Statistically, no difference could be found between disease status of group 1 and 2, but clinically group 2 appeared to be in better health than group 1 (table 1).

The rate at which patients recovered did not significantly increase throughout the CR program in both patient groups. Sample sizes were too small and variety within the HF population too big to detect a significant improvement. Nevertheless, both groups showed a trend toward increasing slopes (fig. 14). However, this trend was more prominent in group 2. This suggests that outdoor CR may positively affect HRR in HF patients.

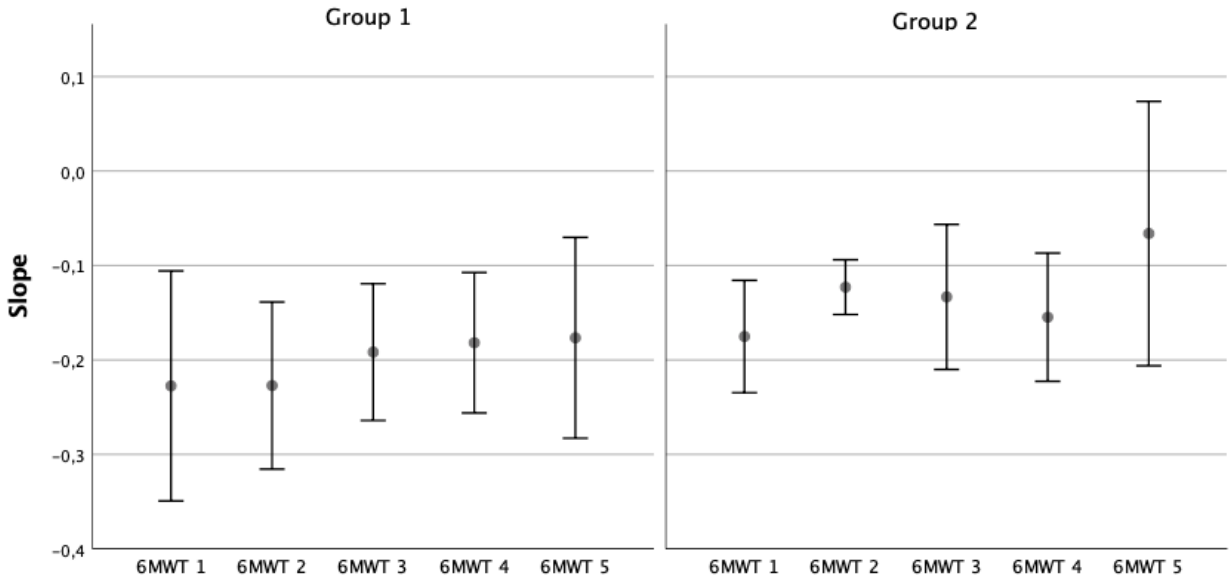

Figure 14. Difference in slope of HRR between group 1 and 2 per measurement.

3.4.5. Heart Rate Variability

Heart rate variability (HRV) during each phase of the 6MWT was compared between group 1 and 2. HRV depends on ECG signal quality. However, because signal quality was poor for multiple measurements, results were not reliable. Moreover, HRV is also strongly dependent on heart rhythm, but in HF patients arrhythmias are not uncommon. Although none of the patients had atrial fibrillation, several patients showed an irregular heart rhythm during one or more measurements or phases of the 6MWT. Many of them presented with extrasystoles, in some at a low frequency and in some at a high frequency. However, it was never a consistent phenomenon. Still, it interfered with HRV outcomes.

HRV represents the interaction between the sympathetic and parasympathetic nervous system on the sinoatrial node. The ability of the autonomic nervous system to dynamically respond to changing situation, thereby altering the intrinsic rhythm of the sinoatrial node, indicates a healthy heart. In HF patients the autonomic nervous system is less responsive and HRV is decreased. As a result, the HF population is at greater risk for mortality. However, research has shown that exercise training, including CR, improves HRV (66). Therefore, it was expected that patients from this study would show an increased HRV as well. Because results were not reliable, this hypothesis cannot be confirmed.

3.5. Outcomes of Questionnaires

There was no significant difference in questionnaire outcome between group 1 and 2. Health change as measured by MLHFQ and SF-36 was similar in both groups and did not significantly differ. In both groups a significant positive difference was seen between disease status before and after the CR program based on MLHFQ outcomes ($p_1 = 0.023$, $p_2 = 0.017$). According to the SF-36, patients improved in several ways. For most of the health concepts, patients of group 1 and 2 showed the same trend. In both patient groups a significant difference or trend toward significance was seen between physical and emotional health before and after the rehabilitation program. However, both groups remained to have emotional problems due to their heart disease. This indicates that patients have a hard time emotionally, more than physically. Indeed, the CR program aids patients to get in better health again, but is insufficient to relieve emotional problems. Nevertheless, emotional wellbeing increased in group 2, but not in group 1. Moreover, group 2, more than group 1, also indicated that their physical health or emotional problems still interfered with their social activities after the rehabilitation program. Furthermore, some contradictory results were found concerning health change in

both group 1 and 2. In some questions patients indicated that they noticed improvements, while in others they did not. These findings show that patients are not fully aware of the improvements they have undergone and that they have difficulty properly estimating their health status. Therefore, it is important to develop an objective system to evaluate health status in HF patients.

4. Conclusion

This pilot study aimed to investigate whether HF patients that participate in CR can be evaluated in the same way outside the hospital as inside the hospital. It was demonstrated that patients that were monitored inside the hospital and those that were monitored outside the hospital equally improved throughout the rehabilitation program, as shown by the increase in 6MWD. More interestingly, it was demonstrated that multiple HR parameters differ in an outdoor setting. Both RHR, max HR and HRR seemed to be subject to environmental changes. RHR appeared to be lower in patients that were monitored outside, while max HR was higher in these patients compared to patients monitored inside the hospital. Additionally, sympathetic-mediated HRR was also increased in patients monitored outside. As a result, the data are not in line with the initial hypothesis that HF patients can be evaluated in the same way outside the hospital as inside the hospital. The current results suggests that outdoor monitoring requires other means of interpretation.

In addition, this study showed that there is a wide variety within the HF population. As a result, HF patients do not equally benefit from a CR program. Moreover, these findings highlight once again that personalized approaches are required in the treatment of HF.

However, there were several limitations to this study. The sample size of the study population was very small and therefore may not be representative of the general HF population. In addition, there were clinical differences between both groups that could have influenced the outcomes. Moreover, because two groups were used that were monitored inside or outside instead of one group in which patients were both monitored inside and outside, it remains uncertain whether the results are truly caused by the different environment. Therefore, for future research it would be interesting to follow up HF patients that perform a test both inside and outside every three weeks. In this way it would be more clear what the effect is of being outdoors. Nevertheless, these results indicate that there may be a difference between indoor and outdoor monitoring, but future research is required to define a true difference.

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6. Scientific Contributions

Feasibility of a multiparametric wearable device to remotely monitor cardiac activity in healthy subjects outside the hospital

1. Introduction

One of the hallmark symptoms of heart failure (HF) is exercise intolerance, which is caused by a low functional capacity (FC). To increase FC, HF patients are encouraged to participate in a cardiac rehabilitation (CR) program. However, only a minority of patients attends CR sessions. A great number of patients is limited in time or transport and therefore is not able to participate in a CR program or experiences a decrease in motivation, which makes them to drop out eventually. To overcome this problem, CR could be organized outside the hospital as well, for example in a public park. Because it is practically impossible to provide the same service during outside CR sessions, it would be interesting to remotely monitor patients with a wearable device. This would allow physicians and physiotherapist to track progression from a distance and would make CR more accessible for HF patients.

2. Methods

2.1. Study Design

This study investigates the ability of a novel multiparametric wearable device to measure cardiac activity in healthy subjects in an outdoor setting. Patients were recruited on a voluntary basis. They were included if they were older than 45 years and did not had any cardiac problems for which a β-blocker, ACE-inhibitor or diuretic would be required. Patients were excluded if they were unable to give informed consent or if they did not master the Dutch language. Other exclusion criteria were orthopedic or neurological limitations. All patients gave their written informed consent. The study complied with the Declaration of Helsinki and the study protocol was approved by the ethical committee of ZOL and Hasselt University (EC 14/085U).

2.2. Experimental Protocols and Statistical Analysis

Subjects were asked to perform one 6MWT inside the hospital and one outdoors, within a period of 2 weeks. The tests were executed on different days, but at the same hour. To get familiar with the protocol of the 6MWT, all subjects were first tested inside the hospital. The remaining procedures and statistical analysis were performed as described previously.

3. Results and Discussion

In total, six subject were included into the study, of which three were male and three were female. The mean age of the study population was 64 ± 11. Mean weight was 73.7 ± 16.2 and mean BMI 26.0 ± 3.6. None of the subjects smoked. This population was similar in age, weight and BMI to the general HF population that participates in a CR program.

There was no significant difference in 6MWD between the indoor and outdoor measurement. P-value was rather low and might indicate a trend toward significance, which would suggest that FC is higher outdoor or increased in a few days. This is very unlikely since these subjects did not follow any physical training program. However, studies have shown that a learning effect may be seen when performing a second 6MWT over a short period of time (1,2). Therefore, the increase is considered to be the result of a learning effect and not the result of the changing environment.

No significant difference in RHR and max HR was seen either. Nevertheless, p-values were low and might decrease if more subjects are included. HRR at minute 1, 2 and 3 after the 6MWT were not significantly different between the indoor and outdoor measurement. However, at minute 3 there was a clear borderline significance. Moreover, at minute 4 and 5 after the 6MWT the difference between indoor and outdoor was significant (table 1). This is in accordance with the previous results and indicates subjects recover better outside than inside.

Table 1. Differences in 6MWD and HR parameters between indoor and outdoor measurement.

	Indoor	Outdoor	p-value
6MWD	600 ± 89	628 ± 108	0.135
RHR	68 ± 8	65 ± 8	0.245
Max HR	117 ± 10	128 ± 16	0.117
HRR min 1	18 ± 6	24 ± 11	0.234
HRR min 2	26 ± 7	33 ± 10	0.159
HRR min 3	38 ± 10	47 ± 11	0.074
HRR min 4	40 ± 9	51 ± 14	0.028
HRR min 5	41 ± 9	52 ± 13	0.014

These results suggest that environment might affect several HR parameters in healthy subjects. Therefore, when remotely monitoring subjects with a wearable device, it is important to consider the subject's environment.

4. Conclusion

This study shows that the novel multiparametric wearable device is able to measure cardiac activity in healthy subjects in an outdoor setting. However, the findings indicate that HR parameters are subject to changes when the environment changes. This must be kept in mind when interpreting the results. Especially in HF patients that participate in a CR program, this is important to determine if they are progressing or not. Therefore, it can be concluded that the wearable device can be used to remotely monitor FC in subjects that are outside, but that results of outdoor measurements cannot be compared with indoor results due to the impact of being outdoors on HR parameters.

5. References

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Feasibility of a multiparametric wearable device to remotely monitor heart failure patients at home

1. Introduction

Heart failure (HF) is one of the most common causes of hospital admission in patients over the age of 65. Moreover, up to 50% of HF patients is rehospitalized within 6 months after their first admission. This imposes a major burden to society and the healthcare system. To prevent rehospitalization of HF patients, it could be interesting to remotely monitor patients with a wearable device. This would allow physicians to evaluate disease status from a distance and anticipate adverse events. Medications could be timely adapted and patients would not further deteriorate, thereby preventing hospital admission.

2. Methods

2.1. Study Design

The current study assesses the feasibility of a multiparametric wearable device to remotely monitor HF patients at home. Patients were recruited on a voluntary basis. They were included if they participated in cardiac rehabilitation (CR) and had a LVEF of less than 55%. Patients were excluded if they were unable to give informed consent or if they did not master the Dutch language. Other exclusion criteria were orthopedic or neurological limitations. All patients gave their written informed consent. The study complied with the Declaration of Helsinki and the study protocol was approved by the ethical committee of ZOL and Hasselt University (EC 14/085U).

2.2. Experimental Protocols and Statistical Analysis

Patients were asked to perform one 6MWT inside the hospital and one at home, within a period of 2 weeks. The tests were executed on different days. The 6MWT inside the hospital was performed before the start of a rehabilitation session. The test at home was performed on a day the patient did not had to attend CR. To get familiar with the protocol of the 6MWT, all patients were first tested inside the hospital. During the test inside the hospital patients were set at rest in a wheelchair. During the test at home patients had to stand still. The 6MWT inside the hospital was performed on a hard, flat and smooth surface in an enclosed corridor. The walking track measured 45 meters in length and was marked every 5 meters. For the at home measurements a walking track was chosen in the neighborhood of the patients' home that was as flat and quiet as possible to reproduce the hospitals walking track as well as

possible. The length of these walking tracks differed for each patient. They were not marked, but the distance was tracked using a smartphone health application. The remaining procedures and statistical analysis were performed as described previously.

3. Results and Discussion

In total, three patients were included into the study, two males and one female. Age ranged between 56 and 71 years old, with a mean of 63 ± 8. Mean weight was 84.3 ± 7.5 and mean BMI was 29.4 ± 1.5. Mean LVEF in this population was 33.5% ± 6.1%. Two patients reported symptoms of NYHA class I and one patient of NYHA class III. All patients received ACE-inhibitors, β-blockers and diuretics and one patient smoked. The population described here is similar in gender, age, weight, BMI and disease status to the general HF population that participates in a CR program.

Table 1. Differences in 6MWD and HR parameters between in hospital and at home measurement.

	In hospital	At home	p-value
6MWD	540 ± 501	527 ± 49	0.612
RHR	59 ± 9	66 ± 10	0.138
Max HR	97 ± 11	98 ± 4	0.773
HRR min 1	16 ± 8	16 ± 5	0.818
HRR min 2	21 ± 8	20 ± 9	0.328
HRR min 3	28 ± 10	25 ± 12	0.201
HRR min 4	32 ± 11	27 ± 12	0.056
HRR min 5	32 ± 12	28 ± 12	0.074

There was no significant difference in 6MWD between both measurements, nor was there a difference in HR parameters (table 1). However, both HRR at minute 4 and 5 after the 6MWT showed a clear borderline significance. The previous results showed that HRR at minute 4 and 5 is higher outdoors than indoors. The current findings suggest the opposite is true. Patients seemed to recover better inside the hospital than at home. However, earlier studies have reported a significant increase in HR in an upright position compared to a supine position (1,2). Because patients were in an upright position during the recuperation at home, it could be that their HR could not decrease as much as during the recuperation inside the hospital when they were in a supine position. This suggests that the perceived differences in HRR may not be a direct result of the environment neither, but rather of the lower HR in supine position during

the test inside the hospital. Therefore it is doubtful whether the perceived differences are true differences.

4. Conclusion

The aim of this pilot study was to assess the feasibility of a multiparametric wearable device to remotely monitor HF patients at home. The results indicate that there is no significant difference between in hospital and at home measurements with the wearable device. This suggests the wearable can be used to remotely monitor health status in HF patients. However, because the sample size was very small, this study only gives an indication. Future research has to investigate whether the perceived differences are due to the environment or other factors, such as body position.

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Supplement

Table 1. Description of NYHA classification.

NYHA Classification	
Class I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
Class IIII	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

Table 2. Borg scale

Score	**Description of Exertion**
0	Nothing at all
0,5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very very severe
10	Maximal

Table 3. Difference in HRR at minute 1 to 5 after the 6MWT between group 1 and 2 per measurement. HRR is expressed in bpm

	Group 1	Group 2	p-value
HRR 1			
Minute 1	11 ± 5	13 ± 8	0.568
Minute 2	17 ± 9	19 ± 9	0.695
Minute 3	21 ± 8	29 ± 10	0.190
Minute 4	22 ± 7	33 ± 10	**0.053**
Minute 5	22 ± 8	35 ± 10	**0.048**
HRR 2			
Minute 1	13 ± 6	12 ± 9	0.815
Minute 2	18 ± 9	19 ± 10	0.841
Minute 3	23 ± 7	31 ± 12	0.190
Minute 4	24 ± 6	37 ± 12	**0.061**
Minute 5	25 ± 6	38 ± 12	**0.055**
HRR 3			
Minute 1	13 ± 6	14 ± 5	0.596
Minute 2	19 ± 7	20 ± 6	0.965
Minute 3	28 ± 10	32 ± 10	0.492
Minute 4	30 ± 10	38 ± 11	*0.195*
Minute 5	32 ± 10	41 ± 13	*0.225*
HRR 4			
Minute 1	14 ± 7	15 ± 7	0.749
Minute 2	20 ± 7	22 ± 8	0.632
Minute 3	29 ± 9	35 ± 11	0.349
Minute 4	31 ± 8	41 ± 10	**0.091**
Minute 5	31 ± 9	44 ± 10	**0.056**
HRR 5			
Minute 1	14 ± 7	17 ± 7	0.548
Minute 2	21 ± 9	22 ± 9	0.798
Minute 3	30 ± 12	33 ± 15	0.787
Minute 4	32 ± 11	41 ± 10	*0.263*
Minute 5	34 ± 12	47 ± 5	**0.057**

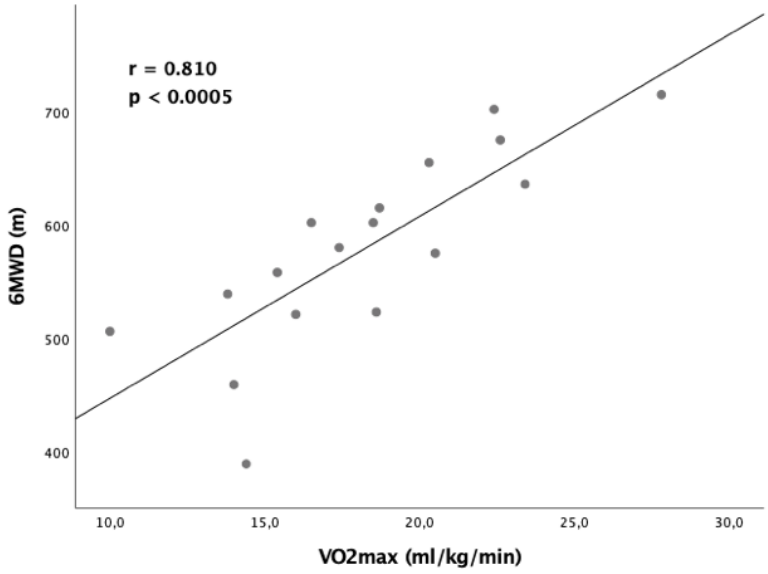

Figure 1. Correlation between 6MWD and VO_2 max.