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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Predictors associated with exercise capacity in HF patients with a CRT device: scoping review & retrospective analysis

Michiel Lanssens

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Paul DENDALE

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Acknowledgment:

First I would like to thank my thesis promotor (Prof Dr. P. Dendale) and co-promotor (M. Scherrenberg) of the Hasselt University to assist me in writing this master thesis. They allowed this thesis to be my own work, but gave me good advice whenever needed.

Secondly, I would like to thank all the other cardiologist and staff members of ‘Hartcentrum Hasselt’ to allow me to perform data extraction in their center and giving me access to their database.

I would also like to thank the Hasselt University for the opportunity of performing scientific research during my masters studies.

Paalsteenstraat 179, 3500 Hasselt; 3/6/2019 M.L.

Research context

This master thesis, made by one master student of the Hasselt University faculty ‘Rehabilitation sciences and physiotherapy’, fits within the research domain ‘rehabilitation of cardiovascular disorders’. This work was supervised by Prof Dr. P. Dendale (promotor) and M. Scherrenberg (co-promotor) of the research group ‘Health Care’.

Last year I performed a literature study, together with another student, about the feasibility of telemonitoring with mobile apps for patients with heart failure (HF) and coronary artery disease while performing a cardiac rehabilitation (CR) program. We concluded that there is a trend towards high feasibility for the usage of mobile apps, but this could not be statistically confirmed because of the lack of high-quality research. This year I am going to do specific research for patients with HF who have been implanted with a cardiac resynchronization therapy device (CRT) and are remotely telemonitored. My main objectives were to get an overview of what possible parameters could be monitored and which are important parameters to predict their exercise capacity after the CRT implantation.

This research is socially relevant because more and more people are being diagnosed with HF and the healthcare burden keeps increasing. Telemonitoring gives the possibility to closely follow-up patients without or with lesser in-clinic visits. Therefore, being time-efficient for the patient and healthcare practitioner and reducing the healthcare cost for the patient. Also, telemonitoring patients gives the healthcare practitioner a more objective overview of physiological parameters over a longer period in comparison to a relatively short check-up during an in-clinic visit.

Study design and method were predetermined by the (co-)promotor. Data acquisition was completely performed by the student and made a complete dataset of which the co-promotor performed the data-analysis. The interpretation of the data-analysis was done by the student. The student wrote the complete thesis on his own, but with guidance of the co-promotor.

Abstract

Background: HF is a chronic condition which progressively affects more people with an increasing healthcare burden.

Objectives: Two parts with different objectives: (1) systematic review of possible parameter that could be telemonitored in HF patients whit a CRT implanted; (2) retrospective analysis of HF patients with a CRT to detect predictors of exercise capacity after a CR program.

Participants: Part I: multiple databases (PubMed, Web of Science, Scopus) were systematically researched. Part II: 100 patients included who performed a CR program between 1/1/2013 and 31/1/2019.

Measurements: Part I: study design, baseline characteristics and telemonitored parameters extracted of all 21 included studies. Part II: socio-demographic and clinical demographics (exercise capacity, device type, type CMP, medication, blood profile) were collected.

Results: Part I: parameters monitored: ITI (n=12), PA (n=9), I-ECG (n=7), HRV (n=3), HR (n=3), pacing rate (n=3), frequency of biventricular pacing (n=3), frequency of ICD/CRT(-D) intervention (n=3), mean 24h HR (n=2), HR at night (n=2), HR at day (n=1), daily min RR (n=1), daily median RR (n=1), daily max RR (n=1), RR (n=1), RR rate based on TI (n=1), relative tidal volume (RTV) (n=1), accelerometer based heart-sounds (n=1). Part II: 31 patients (10% NYHA I, 71% NYHA II, 19% NYHA III) with mean age 65.65years (SD±11.26) and mean EF 38.97% (SD±15.18) had a complete dataset and were analysed. VO2max and peak power both improved significantly ($p<0.001$) by following a CR program. Only gender was a significant predictor ($p=0.04$), for systolic blood pressure at the first session there was a positive trend ($p=0.051$).

Conclusion: Multiple parameters can be monitored through a CRT. Performing a CR program has a significant effect on VO2max and peak power, this effect could be predicted by gender. Also, a trend towards a positive effect of lower systolic BP at the first session.

General introduction

The European Society of Cardiology (ESC) defines heart failure (HF) as a condition in which the heart is unable to pump enough blood through the body for its physiological needs. Typical symptoms of HF are breathlessness, swollen limbs and fatigue[1]. According to data from the ESC approximately 26 million people worldwide have been diagnosed with HF in 2014. This implies that the average prevalence in a country would be around 1-2% of the total population[1]. In 2018 the Belgian Cardiologic Liga (BCL) estimate that more than 16.500 people a year are diagnosed with HF. The BCL predicts that the total number of patients in Belgium could double up to 400.000 patients by 2040[2]. This estimation has a three-layered explanations: (1) increasing prevalence of HF with aging, more than 80% of the patients are 65 years or older; (2) demographic evolution of a population who is constantly living longer; (3) more and more patients with HF survive longer due to better medical care[1]. This care comes at a high economical cost, in Western Europe it accounts for 1-3% of the total budget for healthcare.[1] According to the BCL the total cost of HF in Belgium is 152 million euro in 2018 (2-3%) and is mainly attributed to hospital admissions[2]. Delayed admission and treatment of acute HF with four to six hours after onset of symptoms increases the mortality rate significantly[1]. One of the other problems is that the general knowledge of HF is not as high as for myocardial infarct or stroke. In Belgium approximal 1 out of 4 people know and understand HF and 1 out of 10 can name at least one risk factor[2]. Therefore, awareness of the general population about the disease and its symptoms is important.

CRT implantation is indicated in patients with HF because of cardiac dyssynchrony. This dyssynchrony emerges because of prolongation of the atrioventricular (AV) interval. The prolongation delays systolic contraction and may encroach diastolic filling. Because of this delay left ventricular (LV) diastolic pressure will rise, causing diastolic mitral regurgitation. Thus, causes the loss of the Frank-Starling mechanism and therefore a reduction in LV contractility. This mechanism combined with an inter/intra-ventricular conduction delay, causing asynchronous contraction of the LV wall, impairs stroke volume and systolic blood pressure. CRT restores AV and inter/intra-ventricular synchrony, improves LV function, reduces mitral regurgitation and increases LV filling time and LV ejection fraction (EF)[3]. The implantation of a CRT improves exercise tolerance directly because of an improvement of the cardiac output. Indirectly there will be some peripheral (muscular and vascular) changes if the patient additionally completes a CR program. These changes combined with the improvement of the cardiac function significantly improves: exercise duration, VO2max, peak cardiac power output and cardiac reserve. This however depends on the frequency and duration of the program[4]. One of the main questions about CRT-implantation is: 'Is CRT cost-efficient due to the cost of the devices and limited life expectancy of the recipient?'. Researchers compared CRT to standard medical care and calculated that by using the devices there is a reduction of 50.000-100.000 USD/QALY[5]. Burri et al. (2013) confirms that investing in a home monitoring system is cost neutral in 10 years for the United Kingdom[6]. In their calculations they did not consider the possible reduction of cardiovascular events and patients cost savings (e.g. transportation). Thus, suggesting that this progress will be faster than 10 years.

After a CRT implantation livelong follow-up is necessary. Self-management plays an important role in the total care program of these patients. For example, in diabetes type two De Vos et al. (2013) concludes that self-management has a significant impact on lifestyle[7]. Zamorano et al. (2014) establish that improving self-management in HF patients can reduce the amount of hospital admissions[8], thus a reduction of the healthcare cost. Because of the technological improvements of the last few years, a CRT may be reprogrammed so it can be used for telemonitoring. But according to a study from 2012 by the ESC and the Heart Rhythm Society there are some (dis)advantages to the devices. Two main disadvantages are: technical issues (e.g. lead fracture) and ineffective sensing and pacing, this means that if the device fails to sense properly it could sense an abnormality while there is none and start pacing incorrectly. According to the authors there are some advantages, the main one is earlier detection of clinical problems. Another is that the patients must travel less because of fewer in-clinic visits, which is cost-benefit for the patient[9]. Another advantage is that almost all fabricants build an antenna in their device, therefore creating an opportunity for researchers who can gather easily more data from more patients.[9]

Further research is necessary given following reasons: the growing number of patients with HF, the cost-efficiency of telemonitoring, the earlier detection of abnormal events in HF patients and the large number of parameters that could be monitored. This research should focus on the application and feasibility of telemonitoring programs for HF patient with a CRT. Not only can clinicians telemonitor parameters[1-9] but they can also check if the CRT is still working properly[9]. This master thesis has a double purpose: first we are going to give a scoping review of the literature about possible parameters that can be used during telemonitoring of patients with a CRT, secondly we are going to perform a retrospective analysis of patients with a CRT who completed a CR program to investigate what parameters are important predictors for the exercise capacity (VO2max).

Part I – Scoping review

1. Methods:

The goal of this systematic literature review was to answer the following research question: 'What is already known about physiological parameters that could be telemonitored in patients with HF who have a CRT implanted?'. This question was based on following PICO: (Patient) HF patients with a CRT, (Intervention) telemonitoring, (Comparison) usual care, (Outcome) physiological parameters. We systematically searched three databases (PubMed, Scopus and Web of Science) with the following strategy: 'Heart Failure' AND 'Monitoring, Physiologic' AND ('Cardiac resynchronization therapy' OR 'Pacemaker, artificial' OR 'Defibrillator') and filtered the articles based on date of publication (last 5 years) and level of evidence (LoE) not higher as a randomized controlled trial (RCT). Following inclusion criteria were used: (1) HF patients with a CRT device implanted, (2) telemonitoring, (3) language: Dutch or English; and following exclusion criteria: (1) date of publication: older than 5 years, (2) LoE higher as a RCT. We extracted following data from the included studies: (1) study design; (2) baseline characteristics of the study population: age, New York Heart Association (NYHA) class, number participants; (3) telemonitored parameters.

2. Results:

Based on our search strategy (*table 1. Overview hits databases*) we found 148 studies (112 PubMed, 22 Scopus, 14 Web of Science) across the three databases. From these 148 studies there were 115 unique studies of which we screened title and abstract. From these 115 studies we excluded 94 studies *(table 2. reason exclusion)*. Studies were excluded based on: not meeting inclusion criterium 1 (n=11); not meeting inclusion criterium 2 (n=29); not meeting inclusion criterium 3 (n=10); exclusion criterium 1 (n=10) and exclusion criterium 2 (n=18) *(fig 1 flowchart articles)*.

The results of our data extraction are visible in table 3 *(table 3. data extraction*). The 21 included studies all had a LoE lower than a RCT. The majority (n=15) were observational studies, and the others were: RCT's (n=3), retrospective analyses (n=2) and case report (n=1).

Nine studies[1,3-7,10,16,17] had a complete overview of all the NYHA classes present in their study population. Across these nine the overall population was 3481 patients with a mean NYHA class 2.01 with following distribution: NYHA I n=254 (7.2%), NYHA II n=2210 (63.5%), NYHA III n=1003 (28.8%), NYHA IV n=14 (0.4%). Five studies only mentioned one or two specific NYHA classes of the total study population: D'Onofrio et al. (2018): 91/173 NYHA II-III (53%); Jedrzejczyk-Patej et al. (2014): 14/96 NYHA IV (14.5%); Jedrzejczyk-Patej et al. (2016): 21/304 NYHA class IV (7%); Mazurek et al. (2016): 210/304 NYHA III (69%) and 21/304 NYHA IV (6.9%); Molon et al. (2014): 175/221 NYHA II (79%). Four studies calculated the mean NYHA class for their study population: Liberska et al (2016): 2.75; Malfatto et al (2016): 2.5 (SD 0.7); Suzuki et al (2017): 3.1 (SD 0.6); Vamos et al (2018): 2.42 (SD 0.78). Three studies[11,19,21] did not mention any NYHA class of their population.

In declining order following parameters were monitored and described in the included studies: intrathoracic impedance (ITI) (n=12), patient activity level (PA) (n=9), intracardiac electrocardiogram (I-ECG) (n=7), heart rate variability (HRV) (n=3), heart rate (HR) (n=3), pacing rate (n=3), frequency of biventricular pacing (n=3), frequency of ICD/CRT(-D) intervention (n=3), mean 24h HR (n=2), HR at night (n=2), HR at day (n=1), daily min respiratory rate (RR) (n=1), daily median RR (n=1), daily max RR (n=1), RR (n=1), RR rate based on TI (n=1), relative tidal volume (RTV) (n=1), accelerometer based heart-sounds (n=1).

Six studies[1,3,14, 17,20,21] proposed multiple parameters that could be used for prognostic evaluation of HF patients. Boehmer et al. (2017) enrolled 974 patients (NYHA I 4.5%, NYHA II 69%, NYHA III 25.5%, NYHA IV 1%) during one year. New software was downloaded into the CRT-defibrillator (CRT-D), thus converting it into a sensor research device and allowing data collection from the devices. The data that they collected were: HR, accelerometer-based heart sounds, RR, RTV, ITI and PA. Data is downloaded either during follow-up visits or through remote LATITUDE transmissions. The developed algorithm had a 70% predictive sensitivity of heart failure events (HFE) with a median early warning of 34 days before the HFE. The MULTITUDE-HF study of Forleo et al. (2015) enrolled 124 patients (NYHA I 14%, NYHA II 52%, NYHA III 53%, NYHA IV 1%) who were implanted with an ICD (n=66) or CRT-D (n=58) with the RR trend diagnostic feature. Data was evaluated during in-office follow-up visits at 1, 3 and 6 months and every 6 months thereafter. RR was continuously monitored through low-voltage ITI measurements. They concluded that continuous RR-monitoring may provide valuable indices for the prognosis stratification of HF patients. Mazurek et al. (2016) enrolled 304 patients (69% NYHA III, 6.9% NYHA IV) with a CRT-D who received a portable, wireless transmitter for remote monitoring. All patients were followed 1 week and 1 month after implantation and every 6 months thereafter. Following parameters were monitored: the percentage of biventricular pacing, I-ECG, mean 24h HR and PA. They concluded that daily-based remote monitoring of biventricular pacing should be considered because transient episodes of CRT% loss had a negative effect on prognosis of these patients. During the TELECART study of Sardu et al. (2016), the authors enrolled 183 patients (NYHA II 45%, NYHA III 55%) with and without CRT-D telemonitoring technology and monitored following parameters: I-ECG, pacing rate and PA. They concluded that telemonitoring was a powerful diagnostic tool that can predict hospitalization due to HF. Suzuki et al. (2017) enrolled 21 patients (mean NYHA class 3.1) with a CRT-D. They monitored ITI daily for a mean of 12 months and concluded that a higher rate of change of the decrease of ITI is associated with hospitalization due to worsening HF. Vamos et al. (2018) enrolled 42 patients (mean NYHA class 2.42) with a CRT-D and did a follow-up through the CareLink system for the monitoring of ITI. Patients were followed-up every three months. The authors also tested a new diagnostic algorithm based on PA, HRV, frequency of biventricular pacing, HR at night and concluded that these parameters could improve clinical reliability of the predictive algorithm. A retrospective analysis of 146238 patients (no data about NYHA classes) with a CRT-D or ICD was performed by Zile et al. (2016). The devices were linked to the CareLink system from which they performed their analysis. Following parameter were analysed: ITI and PA.

They concluded that by measuring these parameters it is possible to identify risk stratification in HF patients, especially baseline ITI predicts mortality.

Five studies[6, 7,11, 16, 21] investigated the effect of telemonitoring certain parameters on clinical score and mortality. The IN-time trail of Hindricks et al. (2014) compared telemonitoring (n=333) with standard care (n=331). The patients (NYHA II 45%, NYHA III 55%) in the telemonitoring program received a dual-chamber ICD or CRT-D that is equipped with a Biotronik Home Monitoring function. This function includes that the device, at a set time every day or on detection of tachyarrhythmia, transmits diagnostic data (HR, frequency biventricular pacing, PA and I-ECG). This data is received by a small portable device and transmitted automatically over mobile telephone links. They concluded that automatic, daily, implant-based telemonitoring of rhythmic and technical parameters have a significant beneficial effect on clinical score and mortality. The MADIT-RCT of Jame et al. (2017) randomized 1008 patients (NYHA I 14%, NYHA II 86%) with a CRT-D (n=1089) or an ICD (n=731) into two groups. The percentage of PA in each group was gathered. Group 1 was used for determination of optimal cut-off threshold and group 2 to validate this threshold. They concluded that reduced PA in patients with mild to moderate HF undergoing CRT is a short-term marker of death. During the ALTITUDE activity study of Kramer, Jones, Rogers, Mitchell, & Reynolds (2017), the authors described 26509 patients with a median follow-up time of 2.3 years. They retrospectively analysed patients who were enrolled into the LATITUDE clinical remote monitoring system. The parameter that they analysed was PA through integrated accelerometers in the devices. They concluded that device-detected activity varies widely and predicts survival but did not found a casual mechanism between both. However, they suggested that PA may serve as a useful marker of risk among HF patients. Portugal et al (2016) researched 312 patients with an ICD implanted and analysed two groups: one group (n=121) followed RM and the other group (n=191) were conventionally followed-up in an outpatient setting. The RM-group was monitored for various parameters: frequency of ICD/CRT-D interventions, I-ECG and other non-described parameters. They concluded that RM is associated with a lower incidence of mortality. Zile et al. (2016) concluded that baseline ITI predicts mortality.

Four studies[15-18] researched the effect of measuring parameters on HF decompensation and hospitalization. Molon et al (2014) enrolled 221 patients (79% NYHA II) with a single/dual-chamber ICD. They remotely monitored ITI for an average of 17 months and described a significant reduction of HF-related hospitalizations. According to Portugal et al (2016) RM was associated with a lower incidence of hospitalization for HF. Sardu et al. (2016) concluded that TM was a powerful diagnostic tool that can predict HF hospitalization. Suzuki et al. (2017) established that a rising rate of change in decreasing ITI was associated with hospitalization due to worsening HF.

Four[1,4,5,7] studies specifically investigated the effect of multiple parameters on the prediction of HFE. Boehmer et al. (2017) developed an algorithm with a 70% predictive sensitivity and early warning of 34 days before HFE. Goetze et al (2015) included 120 patients (NYHA I 2.5%, NYHA II 8.5%, NYHA III 89%) with an ICD or CRT-D. The device could register daily maximum, median and minimum RR. Data was collected during 1, 3, 6 and 9-month follow-up visits. They concluded that RR is a predictor for HFE and may be a valuable addition to standard management for HF patients. The study of Gudmundsson, Lynga, Rosenqvist, & Braunschweig (2016) enrolled 43 patients (NYHA II 60%, NYHA III 40%) with a CRT or ICD that permits continuous measurement of ITI. Patients were followed for more than 12 months and visited every second month for device interrogation. Each patient received a digital telemonitoring scale to weight themselves every morning, this data was automatically transferred to a central server. They concluded that impedance monitoring is a sensitive method for predicting HFE with intermediate specificity. Monitoring of bodyweight alone is less sensitive and specific, but the combination of both parameters could reduce the false-detection rate to clinically acceptable levels. According to the MADIT-RCT of Jame et al. (2017) reduced PA in patients with mild to moderate HF undergoing CRT was a short-term marker for HFE.

Three studies investigated the effect of parameters on the prediction of VT tachy-/arrhythmias. Jame et al. (2017) concluded that a reduced PA is a short-term marker for VT tachyarrhythmias. The TRUST-CRT study of Jedrzejczyk-Patej et al. (2014) described 96 patients (NYHA IV 14.5%) with a CRT-D. All patients were followed-up after 1 week, 1, 3 and 6 months and every 6 months thereafter. Following parameters were measured: HR during day- and night-time, daily PA, ITI and HRV. They concluded that the combination of multiple parameters improves their predictive performance of VT arrhythmia. Jedrzejczyk-Patej et al. (2016) enrolled 304 patients (NYHA IV 7%) with a CRT-D. Everyone received a portable, wireless transmitter for their implanted device. Following parameters were monitored: I-ECG, frequency of biventricular pacing, HRV and ITI). Patients were also routinely followed-up after 1 week and 1 month after the implantation and every 6 months thereafter. They concluded that atrial arrhythmias occurred in two-thirds of CRT-D patients within 2.5y after implantation.

Two studies performed research on the use of ITI-measurements. Kirchner, Paule, Beckendorf, Achenbach, & Arnold (2015) enrolled 53 patients (NYHA I 13%, NYHA II 65%, NYHA III 16%, NYHA IV 2%) with an ICD. The devices measured ITI and data was transmitted through the Home Monitoring telemedicine system to an automated service centre. Every patient was monitored for 1 year. They concluded that the time of the day that ITI is measured had a significant impact on the results of ITI measurements. In the study of Malfatto et al. (2016), the authors included 70 patients (mean NYHA class 2.5) with an ICD-D with the CareLink function. And analysed the relationship between ITI measurements through the CRT-D device and trans-thoracic impedance. They concluded that there is a strong relationship between both, and that trans-thoracic impedance may be a good alternative for HF patients with preserved ejection fraction because ICD or CRT-D implementation is not recommended for them.

The DASAP-HF study of D'Onofrio et al. (2018) was the only study that investigated the effect of telemonitoring on sleep apnea. In their study 173 patients (NYHA II-IV 53%) were implanted with an ICD or CRT-D with the ApneaScan diagnostic feature. Through this feature it was possible to detect RR and apnea-hypopnea based on ITI that was measured through a low voltage signal. Data is collected after one month during an in-clinic visit. They concluded that by adding this feature to an ICD or CRT-D it is possible to screen patients at risk of severe sleep apnea.

Feasibility of telemonitoring was only described in the study of Liberska et al. (2016). 305 patients (mean NYHA class 2.5) with a CRT-D were enrolled. Patients received transmitters enabling remote monitoring of: HR, I-ECG, frequency of CRT-D interventions, mean 24 HR and pacing rate. They concluded that remote monitoring is feasible, safe and effective.

Vamos, Bogyi, Duray, Nyolczas & Hohnloser (2017) described a case-report of a patient monitored through the wireless CareLink system (Medtronic). They described only following monitored parameters: frequency of ICD interventions and I-ECG.

3. Discussion:

In this systematic review there were mainly observational studies included (n = 15) and only three RCT's. Because of the lack of high LoE studies, this review is of lesser quality. A possible explanation could be that telemonitoring, especially telemonitoring HF patients, is a relative new research area which explains the low number of high LoE studies. The overall power of the included studies was high because all 21 included studies had a relatively big number (n>30) of patients included, except the observational study of Suzuki et al. (2016) (n=21) and the case study[19] (n=1). There was also some heterogeneity in the way that telemonitoring was established, some studies (n=8) performed telemonitoring through daily transmissions while other studies (n=6) collected data during predetermined follow-up visits. One of the main concerns about telemonitoring is the feasibility of the system, only Liberska et al. (2016) researched the feasibility and concluded that telemonitoring is feasible and safe. More studies are necessary to confirm their conclusion.

This review has some strengths and weaknesses. The strengths are: (1) the researcher used a structured search strategy in multiple databases. Therefore, more studies were screened; (2) the researcher worked in a structured way, which increases the validity of this review; (3) the review was performed in a relative new research area. The weaknesses are: (1) only one researcher performed the screening and data analysis of all the studies; (2) only 0.4% of all patients had NYHA class IV, therefore the results are less generalizable for this part of the total HF population; (3) the heterogeneity of measured parameters was high.

We established that we can measure multiple parameters in HF patients, for further research we recommend to not only research the effectivity of the telemonitoring system but also the feasibility and acceptability.

4. Conclusion:

We established that there are multiple parameters that can be measured through a CRT and can be (tele)monitored in different ways (follow-up visits or daily transmissions). Based on one study we can conclude that there is a trend to high feasibility of telemonitoring, but further research is necessary to confirm this.

Part II – Retrospective analysis

1. Introduction

It is well established in literature that physical activity is crucial in the secondary prevention of cardiovascular patients[1]. Especially, patients with recently implanted ICD/CRT devices benefit from participation in CR programs[2]. Participation in these programs can reduce their risk for a future ICD-shock. Research demonstrates that moderate physical activity during leisure time is safe and clinically recommended for most patients with ICD/CRT's[3]. Furthermore, Martens et al. established that following a CRT implantation, the participation in a structured CR program is safe and beneficially influences symptomatic response and clinical outcome. CR has been shown to improve exercise capacity, functional status, quality of life and reduces the occurrence of hospitalizations due to HF and mortality in patients with HF with reduced ejection fraction[5-8]. In patients with HF, higher exercise capacity has been associated with higher survival[9]. CR attributes to partial restoration in endothelial function and skeletal muscle abnormalities. It is well established that the exercise capacity after CR is associated with several factors, including age[10], quadriceps strength during knee extension[11-12] muscle mass[13] haemoglobin (Hb)[14], brain natriuretic peptide (BNP)[15], C-reactive protein (CRP)[16], and renal function[17]. However, it remains unclear which factors predict improvements in exercise capacity during CR. Clarifying this issue is important to enhance the quality and efficiency of CR. The purpose of this study was to elucidate the potentially different predictors of improvements in exercise capacity after CR in patients with recent cardiac resynchronization therapy.

2. Methods

Participants

This study was a retrospective cohort study carried out in Hartcentrum Hasselt, Belgium to investigate the predictors of exercise capacity in patients with CIED's after a CR program phase II. Phase II CR is defined as the secondary prevention center-based intervention performed with the aim of clinical stabilization, risk stratification, and promotion of a long-term health status; and this following the index cardiovascular disease event. Patients will be included when they have finished CR between 1 January 2013 and 31 January 2019.

Procedure

The first objective of the study was to investigate which of the predictors is associated with the exercise capacity after the CR program. Second objective is to investigate which parameters significantly changed between the start and the end of the cardiac rehabilitation program. All data will be derived from the patients file in the database. Several baseline demographics will be analysed *(table 4. Baseline demographics*). These will include socio-demographical and clinical baseline demographics. Data about the patients exercise capacity will be derived from ergospirometry test that the patients performed at the start and the end of the CR program.

Data-analysis

Analyses of the data will be performed with SPSS (version 25) software in the Department of Medicine & Life Sciences (Hasselt University. Data from patients with a complete dataset will be used, no data imputation will be performed for missing values. Continuous variables were displayed as a mean and standard deviation if they were normal distributed. Qualitive variables were expressed in terms of percentage. HR% predicted value, power and VO2max at baseline and at the end of the CR program were compared with a paired t-test if the data were normal distributed. A stepwise approach for a multiple linear regression was used to determine independent predictors of VO2max. We applied a significance level of 0.05 for statistical tests.

3. Results:

We included 100 patients of which we could only analyse 31 patients with a complete dataset. Baseline ergospirometry were performed between 12/5/2016 and 12/9/2018, ergospirometry at the end of the CR program were performed between 1/7/2016 and 17/1/2019.

All the results of the baseline demographics are visible in table 5 (*table 5. results baseline demographics)*. Of the total population (n=31) 24 (77%) patients were men and seven (23%) women with a mean age of 65.65 (SD±11.26). Mean BMI was 26.78 (SD±3.38), indicating that the population had overweight. Seven (23%) patients had a BMI higher as 30, which means that they are obese. The left ventricular ejection fraction (EF) had a mean of 38.97% (±15.18), meaning that the population had mild HF with reduced EF. Eighteen patients had an EF below 35%, indicating that they had severe HF with reduced EF. Following NYHA classes were present in the study population: 3 patients (10%) with NYHA I, 22 patients (71%) with NYHA II and 6 patients (19%) with NYHA III. Of the total population 15 patients (52%) had left bundle tack block (LBTB). Patients were implanted with a CRT for 11 different reasons, in declining order: 7 with ischemic cardiomyopathy (CMP) (23%), 7 with non-ischemic CMP (23%), 4 with brady-tachy syndrome (13%), 3 with dilatation CMP (10%), 2 with atrioventricular block (AVB) grade 3 (6%), 2 with total AVB (6%), 2 with sinus arrest (6%), 1 with LBTB with asynchrony (3%), 1 with sick sinus syndrome (3%), 1 with sudden cardiac death (3%) and 1 with hypertrophic CMP (3%). Four different device types were implanted: mostly Boston Scientific (n=11, 35%) and St-Jude (n=10, 32%) were implanted, also Biotronic (n=5, 16%) and Medtronic (n=5, 16%) were used. Mean total cholesterol was 159.29mg/dl (±42.16) indicating that the cholesterol level was acceptable, only four patients had a value above 200mg/dl. If we analyse closer for LDL and HDL we did find a slightly different trend: mean LDL was 101.68mg/dl (±42.31) which is just above the norm value of 100mg/dl and 16 patients had a LDL value above this; mean HDL was 53.42mg/dl (±15.65) which is positive for the cardiovascular risk profile (above the norm value of 40mg/dl), only three patients had a value under 40mg/dl. Mean estimated glomerular filtration rate (eGFR) was 38.97ml/m (±15.18). Only five patients had a haemoglobin A1c (HbA1c) value above 6%, indicating that they were diabetic, mean HbA1c value of the study population was 5.73% (±0.67). Mean Hb value was 13.40g/dl (±1.49), with 13.45g/dl for the men and 13.21g/dl for the women. Four types of medications were analysed. 58% of the patients took ACE-inhibitors, 45% aldosterone antagonist medication, 74% B-blockers, 29% loop diuretics. Only three patients took all four types of medications. Blood pressure (BP) was measured during first training session in 20 patients with a mean systolic BP of 12.05 mm Hg (±1.36) and mean diastolic BP of 6.8 mg Hg (±1.11). During both ergospirometry test HR peak in % of predicted, peak power and VO2max was measured. We performed paired t-test (data was normally distributed) to determine if there was a significant improvement in these three parameters. Only mean HR peak% did not differ significantly ($p=0.0609$) between baseline (mean 115.23±27.69) and at the end (mean 119.61±25.87). Both mean peak power in watt (baseline: 121.77±48.77, end: 145.42±60.36) and VO2max in ml/kg/min (baseline: 18.79±5.21, end: 20.67±6.13) did differ significantly (both $p<0.0001$). In the multiple linear regression, there was only one significant predictor gender ($p=0.040$) for this change in VO2max between baseline and the end of the CR program. Systolic blood pressure approached the significance level 0.05 ($p=0.051$) indicating that a lower systolic blood pressure could be a positive predictor for VO2max at the end of the CR program.

4. Discussion:

Our analyses showed that performing a CR program had a significant effect on VO2max and peak power. And that only gender was a significant predictor of VO2max next to a positive trend of lower systolic blood pressure. It is well established in the literature that exercise capacity or VO2max is a significant predictor of HF mortality or hospitalization: O'Connor, Whellan et al. (2009) concluded that exercise training (thus improving VO2max) was associated with modest reductions for all-cause mortality or hospitalization; Keteyian, Patel et al. (2016) concluded that VO2 max has the strong ability to predict and discriminate mortality in HF patients, they also concluded that prognosis associated with a given VO2 max significantly differed by sex. This analysis confirmed this difference in VO2max by sex and that there was a different (non-statistical) positive effect on VO2max between men and women: mean baseline VO2max women: 15.2ml/kg/min (SD±2.35) and increased with 0.94ml/kg/min (SD±0.82); mean baseline VO2max men: 19.83ml/kg/min (SD±5.37) and increased with 2.16ml/kg/min (SD±2.57). This non-statistical difference in increased VO2max may be explained by the low percentage of women that were included in the study.

The patient population of who these results were derived had some specific demographics. The mean age of the patients was 65.65 years. This corresponds with earlier literature of Conrad, Judge et al. (2018) that says that 80% of HF patients are 65 years or older, meaning that this study population represents the general HF population. Only 23% of the included patients were women, Huffman, Berry et al. (2013) established that the lifetime risk of developing HF of white American women at the age of 45 through 95 is 32-39%. The Rotterdam Heart study of Bleumink, Knetsch et al. (2004) also researched the lifetime risk and they find a 29% risk for women. Thus, both articles indicate that the percentage women with HF in our study was too low.

Generally cardiovascular patients are advised to lose weight, Aune, Sen et al. (2016) confirms this guideline by stating that both having overweight or being obese are associated with increased risk of developing HF. This would explain why the mean BMI of our patients was 26.78 with 23% of them being obese. However, Oga and Eseyin (2016) performed a systematic review about the ‘obesity paradox’ in HF patients. They concluded that patients with overweight and obesity below 40kg/m² have a better prognosis and that the recommendation to lose weight should be given to patients with a BMI above 40.

The average patient had a specific lipid profile, if we look at total lipid count (159.29 mg/dl) we could say that the lipid profile is good. This conclusion could also be drawn from the mean HDL count (53.42 mg/dl). However, the mean LDL count (101.68 mg/dl) slightly indicates hyperlipidaemia. There also exist a 'cholesterol paradox': Konishi and von Haehling (2017) performed a review and stated that HF patients with a higher cholesterol levels are associated with better outcomes.

Of the study population 16% of the patients were diabetic, meaning they had a HbA1c value above 6%. According to Lehrke and Marx (2017) the prevalence of HF in diabetes is high (31%), which would explain why one out of six patients in this study had diabetes. They also stated that the prognosis of HF for these patients is worse. However also for diabetes, as for BMI and cholesterol, there exist a paradox: Aguilar, Bozkurt et al. (2009) concluded that the association between mortality and HbA1c level is U-shaped, with lowest mortality between 7.1% and 7.8%; Eshaghian, Horwich et al. (2006) stated that elevated HbA1c levels are associated with improved survival in patient with diabetes and advanced HF.

CRP can be used to predict systolic HF according to Stumpf, Sheriff et al. (2017), this would explain the elevated CRP (mean 7.89mg/l) in the study population. Also, according to Kang, Fang et al (2017) a higher CRP value is associated with more severe HF.

Also, the four types of medication that patients took were analysed: ACE-inhibitors, aldosterone antagonist, B-blocker and loop diuretics. B-blockers are prescribed because they reduce HR and mortality in HF patients, according to McAlister, Wiebe et al. (2009) every HR reduction of 5 beats/min decreases mortality with 18%. In this study population there was no significant improvement in HR after performing a CR program, this could be explained by the fact that 74% of the study population took B-blockers, thus lowering their HR.

If we look at this study, there are some weaknesses and strengths. The main weakness is that of the 100 included patients, only 31 had a complete dataset which confounds the power of the statistical analyses. Secondly, of these 31 patients none had NYHA class IV, therefore the results of this retrospective analysis are not generalizable for this subgroup of HF patients. Thirdly, as we stated above the percentage of women in this study was too low. And at last, the complete data extraction and analysis was performed by only one student. Although we could only analysis 31 patients, there were eleven different reasons why patients were implanted with CRT which is a broad spectrum. Also 4 types of devices and 4 types of often prescribed medications were analysed in the analysis, adding to the generalizability of the analysis. Also, as we stated above the mean ages complies with the general HF population.

5. Conclusion:

Our retrospective analysis evinced two things for HF patients with a CRT implanted who participated in a CR program: (1) they experienced a significant effect of this program on VO2max and peak power; (2) this effect on VO2max could be significantly predicted by their gender. We also found a trend ($p>0.05$) towards the positive effect of a lower systolic blood pressure at the first session on VO2max at the end of the CR program.

General conclusion

First, we can conclude, based on the systematic review, that multiple parameters can be observed through an implanted CRT in patients with HF. Secondly, based on the retrospective analysis, we can conclude that performing a CR program for HF patients had a positive effect on their exercise capacity. Exercise capacity has been proven to be an important predictor of survival for HF patients. This aspect compared with both other conclusions, makes us conclude that HF patients with a CRT are ideal for telerehabilitation based on their CRT. But further research into feasibility of telerehabilitation of these patients is necessary.

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2. Part I – Scoping review:

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Addendum:

1. Inventory form

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UHASSELT
KNOWLEDGE IN ACTION

INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
27/9/'18	Wijziging MP deel 2 opsplitsing studenten in elk apart deel	Promotor: Copromotor/Begeleider: M. Scherrenberg Student(e): Lanssens Michiel Student(e):
10/12/'18	Wijziging MP deel 2 tot pilot study	Promotor: Copromotor/Begeleider: M. Scherrenberg Student(e): Lanssens Michiel Student(e):
14/3/'18	Wijziging MP deel 2 tot retrospectieve analyse met uitgebreide literatuur	Promotor: Copromotor/Begeleider: M. Scherrenberg Student(e): Lanssens Michiel Student(e):
6/5/'18	- Feedback geleverde werk - Bespreking statistische analyse	Promotor: Copromotor/Begeleider: M. Scherrenberg Student(e): Lanssens Michiel Student(e):
24/5/'18	- Bespreking discussie - ondertekening formulieren	Promotor: Copromotor/Begeleider: M. Scherrenberg Student(e): Lanssens Michiel Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):

In te vullen door de promotor(en) en eventuele copromotor aan het einde van MP2:

Naam Student(e): Michiel Lanssens **Datum:** 03/06/2019

Titel Masterproef: Predictors associated with exercise capacity in HF patients with a CRT devic scoping review & retrospective analysis

1) Geef aan in hoeverre de student(e) onderstaande competenties zelfstandig uitvoerde:
   - NVT: De student(e) leverde hierin geen bijdrage, aangezien hij/zij in een reeds lopende studie meewerkte.
   - 1: De student(e) was niet zelfstandig en sterk afhankelijk van medestudent(e) of promotor en teamleden bij de uitwerking en uitvoering.
   - 2: De student(e) had veel hulp en ondersteuning nodig bij de uitwerking en uitvoering.
   - 3: De student(e) was redelijk zelfstandig bij de uitwerking en uitvoering
   - 4: De student(e) had weinig tot geringe hulp nodig bij de uitwerking en uitvoering.
   - 5: De student(e) werkte zeer zelfstandig en had slechts zeer sporadisch hulp en bijsturing nodig van de promotor of zijn team bij de uitwerking en uitvoering.

Competenties	NVT	1	2	3	4	5
Opstelling onderzoeksvraag	O	O	O	☒	O	O
Methodologische uitwerking	O	O	O	☒	O	O
Data acquisitie	O	O	O	O	☒	O
Data management	O	O	O	O	☒	O
Dataverwerking/Statistiek	O	O	O	☒	O	O
Rapportage	O	O	O	O	☒	O

2) Niet-bindend advies: Student(e) krijgt toelating/~~geen toelating~~ (schrappen wat niet past) om bovenvermelde Wetenschappelijke stage/masterproef deel 2 te verdedigen in bovenvermelde periode. Deze eventuele toelating houdt geen garantie in dat de student geslaagd is voor dit opleidingsonderdeel.

3) Deze wetenschappelijke stage/masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) openbaar verdedigd worden.

4) Deze wetenschappelijke stage/masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) opgenomen worden in de bibliotheek en docserver van de UHasselt.

Datum en handtekening Student(e)

Datum en handtekening promotor(en)

Datum en handtekening Co-promotor(en)

03/06/2019

2. tables and figures - Part I: scoping review

Table 1. Overview hits databases

Search terms PubMed		**Hits March 2019**	**Hits June 2019**
#1	Heart failure	20.289	20.354
#2	Monitoring, physiologic	30.478	30.507
#3	Cardiac resynchronization therapy	1.580	1.636
#4	Pacemaker, artificial	2.719	2.738
#5	Defibrillator, implantable	3.176	3.205
#6	#1 AND #2	574	580
#7	#3 OR #4 OR #5	6.041	6.060
#8	#6 AND #7	120	122
Search terms WOS		**Hits March 2019**	**Hits June 2019**
#1	Heart failure	263.458	263.830
#2	Monitoring, physiologic	4.218	4.261
#3	Cardiac resynchronization therapy	12.308	12.355
#4	Pacemaker, artificial	1.009	1.022
#5	defibrillator	25.875	25.906
#6	#1 AND #2	175	182
#7	#3 OR #4 OR #5		35.679
#8	#6 AND #7	13	14
Search terms Scopus		**Hits March 2019**	**Hits June 2019**
#1	Heart failure	409.798	409.841
#2	Monitoring, physiologic	52.189	52.222
#3	Cardiac resynchronization therapy	14.047	14.076
#4	Pacemaker, artificial	39.899	39.959
#5	defibrillator	37.005	37.104
#6	#1 AND #2	2.403	2.428
#7	#3 OR #4 OR #5	8.165	8.204
#8	#6 AND #7	19	22

Table 2. Data extraction

Author	Study design	Baseline characteristics			Telemonitored parameters
		Age (mean, (SD))	NYHA class (n (%))	Number participants	
Boehmer et al. (2017)	Observational study	66,8 (10,3)	I: 44 (4,5) II: 623 (69) III: 297 (25,5) IV: 10 (1)	974	• HR • Accelerometer-based heart sounds • RR • ITI • PA • RTV
D'Onofrio et al. (2018)	Observational study	68 (10)	II-III: 91 (53)	173	• ITI
Forleo et al. (2015)	Observational study	70 (11)	I: 17 (14) II: 65 (52) III: 41 (33) IV: 1 (1)	124	• RR based on ITI
Goetze et al. (2015)	Observational study	66,3 (10,6)	I: 3 (2,5) II: 10 (8,5) III: 107 (89)	120	• Daily maximum RR • Daily median RR • Daily minimum RR
Gudmundsson, Lynga, Rosenqvist, & Braunschweig (2016)	Observational study	65 (10)	II: 26 (60) III: 17 (40)	43	• ITI • Body weight
Hindricks et al. (2014)	RCT	65,3 (9,6)	II: 285 (43) III: 378 (57)	664	• HR • Frequency biventricular pacing • I-ECG • PA
Jame et al. (2017)	Observational study	/	I: 128 (14) II: 870 (86)	1008	• PA

Table 2. Continued

Jedrzejczyk-Patej et al. (2014)	RCT	62 (6)	IV: 14 (14,5)	96	• Day HR • Night HR • ITI	• PA • HRV
Jedrzejczyk-Patej et al. (2016)	Observational study	65 (11,7)	IV: 21 (7)	304	• I-ECG • Frequency of biventricular pacing	• ITI • HRV
Kirchner, Paule, Beckendorf, Achenbach, & Arnold (2015)	Observational study	66 (11)	I: 7 (13) II: 36 (65) III 9 (16) IV: 1 (2)	53	• ITI	•
Kramer, Jones, Rogers, Mitchell, & Reynolds (2017)	Observational study	70,2 (11)	/	26.509	• PA	•
Liberska et al. (2016)	Observational study	62,6	Mean class: 2,75	305	• HR • I-ECG • Mean 24h HR	• Pacing rate • Frequency of ICD/CRT(-D) interventions
Malfatto et al. (2016)	Observational study	71 (9)	Mean class: 2,5 (0,7 SD)	70	• ITI	•
Mazurek et al. (2016)	Observational study	65 (6)	III: 210 (69) IV: 21 (6,9)	304	• CRT-D pacing rate • I-ECG	• PA • Mean 24h HR
Molon et al. (2014)	Observational study	66 (11)	II: 175 (79)	221	• ITI	•
Portugal et al. (2016)	Retrospective analysis	57,1 (1,2)	I: 55 (17,5) II: 212 (68) III: 43 (14) IV: 2 (0,5)	312	• I-ECG • Other non-described parameters	• Frequency of ICD/CRT(-D) interventions
Sardu et al. (2016)	RCT	72,2 (7,2)	II: 83 (45) III: 100 (55)	183	• I-ECG • Pacing rate	• PA

Table 2. continued

Suzuki et al. (2017)	Observational study	70 (12)	Mean class: 3.1 (0,6)	21	• ITI	
Vamos, Bogyi, Duray, Nyolczas, & Hohnloser (2017)	Case report	69	/	1	• Frequency ICD/CRT(-D) interventions	• I-ECG
Vamos et al., (2018)	Observational study	64 (11,7)	Mean class 2,42 (0,78)	42	• ITI • Frequency of biventricular pacing	• HRV • HR night • PA
Zile et al. (2016)	Retrospective analyse	67 (12)	/	146.238	• PA	• ITI

I-ECG: Intracardiac electrogram; ITI: = intrathoracic impedance; HR: heart rate; PA: patient activity level; RCT: randomized controlled trail; RR: respiration rate; RTV: relative tidal volume

Table 3. Reason exclusion

Reason exclusion	N	Articles
Not meeting inclusion criterium 1	11	Au-Yeung, Reinhall et al. (2015); Barbieri, Dichtl et al. (2018); Bartoli, Vessels et al. (2013); Burri, Sticherling et al. (2013); Goetze, Zhang et al. (2015); Hindricks, Elsner et al. (2014); Maeda, Sakurai et al. (2016); Morgan, Dimitrov et al. (2014); Nunez, Llacer et al. (2016); Ucar, Yilmaztepe et al. (2017); (Wilson, Zeb et al. 2016)
Not meeting inclusion criterium 2	29	Aktas, Mittal et al. (2016); Bansch, Bonnemeier et al. (2015); Bartoli, Vessels et al. (2013); Boriani, Da Costa et al. (2017); Burri, da Costa et al. (2018); Burri, Sticherling et al. (2013); Capucci, De Simone et al. (2017); Guedon-Moreau, Finat et al. (2015); Hansen, Loges et al. (2018); Hernandez-Madrid, Facchin et al. (2017); Hindricks, Elsner et al. (2014); Hindricks, Taborsky et al. (2014); Kaplan, Ziegler et al. (2017); Maeda, Sakurai et al. (2016); Melczer, Melczer et al. (2017); Moffett, Valdes et al. (2013); Morgan, Dimitrov et al. (2014); Muller, Goette et al. (2013); Ogano, Iwasaki et al. (2013); Ozmete, Bali et al. (2016); Padeletti, Botto et al. (2015); Pedersen, Skovbakke et al. (2018); Ricci, Pignalberi et al. (2014); Traulle et al. (2013); Varma, Pavri et al. (2013); Zabel, Vollmann et al. (2013)
Not meeting inclusion criterium 3	10	Aktas, Huang et al. (2013); Burri, da Costa et al. (2018); Hattori, Maeda et al. (2017); Kurek, Tajstra et al. (2017); Maeda, Sakurai et al. (2016); Maurer, Adamson et al. (2015); Morgan, Kitt et al. (2017); Ogano, Iwasaki et al. (2013); Ricci, Pignalberi et al. (2014); Vamos, Nyolczas et al. (2018)
Exclusion criterium 1	18	Adamson (2005); Adamson, Kleckner et al. (2003); Adamson, Smith et al. (2004); Auricchio, Stellbrink et al. (1999); Bosch, Krause-Allmendinger et al. (2009); Bourge (2006); Brignole, Menozzi et al. (1998); (Bruggenjurgen, Israel et al. (2012) ; Carey and Pelter (2007); Conraads, Tavazzi et al. (2011); Himbert, Lascault et al. (1992); Javelle, Paule et al. (2011); Makarov, Belozerov Iu et al. (1993); Lampert, Soufer et al. (2007); Sasaki, Niwano et al. (2007); Sweeney and Prinzen (2006); Vanderheyden, Houben et al. (2010); Wedekind and Moller (2007)
Exclusion criterium 2	26	Bansch, Bonnemeier et al. (2015); Bartoli, Vessels et al. (2013); Capucci, De Simone et al. (2017); Daoud and Houmsse (2016); Dierckx, Houben et al. (2014); Guedon-Moreau, Finat et al. (2015); Haines, Wong et al. (2017); Kurek, Tajstra et al. (2017); Luca, Biscottini et al. (2018); Maeda, Sakurai et al. (2016); Marijon, Jacob et al. (2010); Michalik, Cacko et al. (2018); Molon, Zanotto et al. (2014); Muller, Goette et al. (2013); Nunez, Llacer et al. (2016); Ošmera and Bulava (2014); Ozmete, Bali et al. (2016); Padeletti, Botto et al. (2015); Pedersen, Skovbakke et al. (2018); Ruwald, Aktas et al. (2018); Sciaraffia, Ginks et al. (2013); Wang (2007)

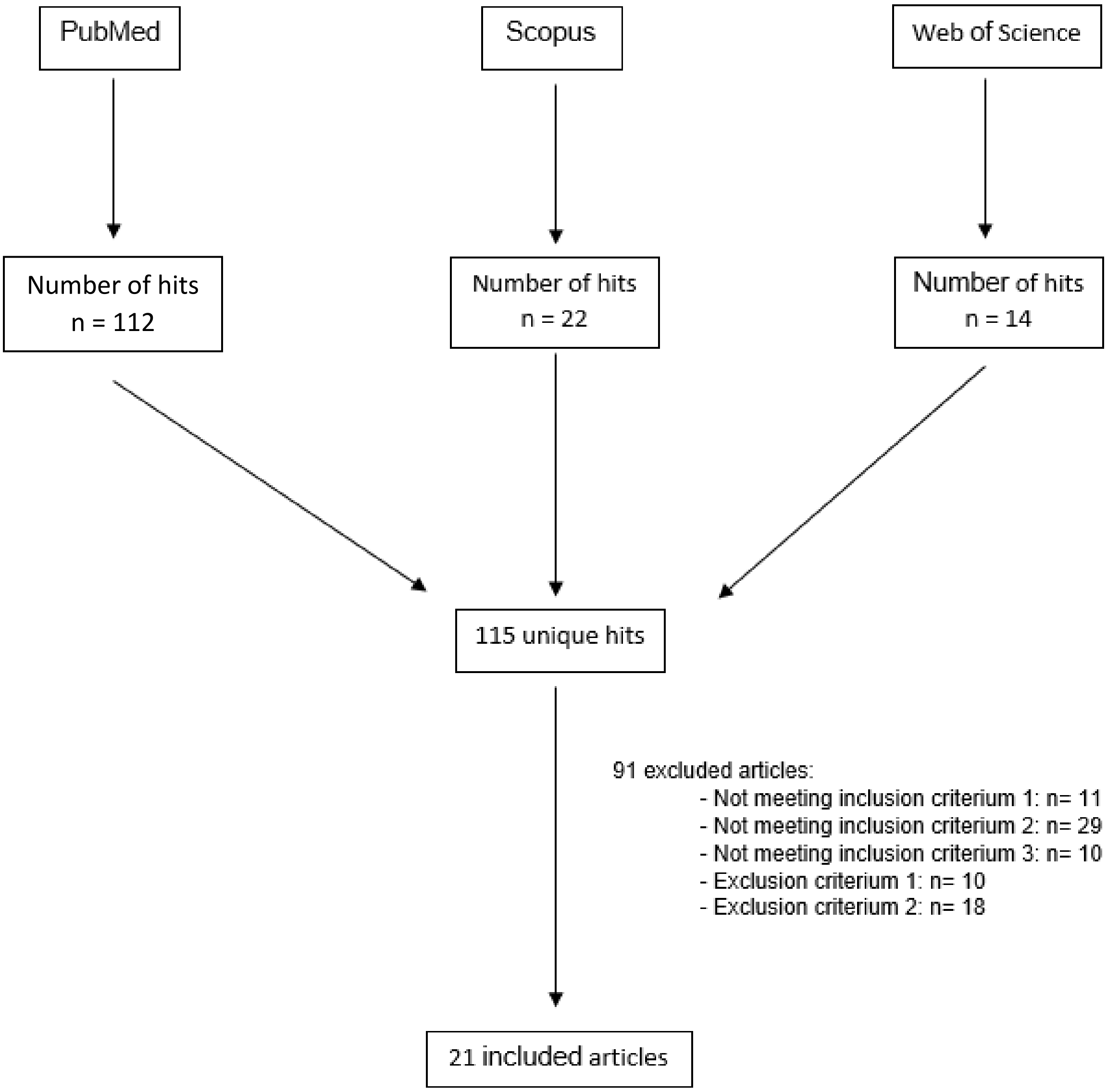

Fig 1. Flowchart

3. tables and figures - Part II: retrospective analysis

Table 4. Baseline demographics

Socio-demographical	
	Patient age (in years)
	Patient gender (Male, Female)
Clinical baseline	
	ACE-I or ARB (yes/no)
	Aldosterone antagonist (yes/no)
	Beta-blocker (yes/no)
	Body mass index (kg/m^2)
	Brain natriuretic peptide (pg/ml)
	C-reactive protein (mg/l)
	Device type
	Diastolic blood pressure in first training session (mmHg)
	Estimated glomerular filtration rate (ml/min)
	Haemoglobin (g/dl)
	HbA1c (in %)
	Heart rate peak and (%) of predicted
	LBBB (yes/no)
	Left ventricular ejection fraction (EF) (%)
	Length (cm)
	Loop diuretics (yes/no)
	NYHA class (I-IV)
	Peak power (watt)
	Smoking behaviour (current, prior, non-smoker)
	Systolic blood pressure in first training session (mmHg)
	Total amount of sessions
	Total cholesterol, LDL-c, HDL-c (mg/l)
	Type of heart failure
	VO2 max (ml/kg/min)
	Weight (kg)

Table 5. Results Baseline demographics

Patient gender (%Male)	77
Patient age (mean±SD	65.65±11.26
BMI (mean±SD)	26.78±3.38
Smoking behavior (%)	
Current	7
Prior	45
Non	48
Left ventricular ejection fraction in % (mean±SD)	38.97±15.18
NYHA class (%)	
I	10
II	71
III	19
LBBB (%yes)	52
Type of heart failure (%)	
Ischemic CMP	23
Non-ischemic CMP	23
Brady-tachy syndrome	13
Dilatation CMP	10
3 grade AVB	6
AVB	6
Sinus arrest	6
LBTB with asynchrony	3
Sick sinus syndrome	3
Sudden cardiac death	3
Hypertrophic CMP	3
Device type (%)	
Boston Scientific	35
St-Jude	32
Biotronic	16
Medtronic	16
Total cholesterol in mg/dl	159.29±42.16
LDL-c in mg/dl (mean±SD)	101.68±42.31
HDL-c in mg/dl (mean±SD)	53.42±15.65
C-reactive protein (mean±SD)	7.89±9.23
eGFR (mean±SD)	38.97±15.18
Haemoglobin (mean±SD)	13.40±1.49
HbA1c (mean%±SD)	5.73±0.67
ACE-I or ARB (%yes)	58
Aldosterone antagonist (%yes)	45
Beta-blocker (%yes)	74
Loop diuretics (%yes)	29
Systolic blood pressure in first training session (mean±SD)	12.05±1.36
Diastolic blood pressure in first training session (mean±SD)	6.8±1,11
Heart rate peak in % of predicted at baseline (mean±SD)	115.23±27.69
Heart rate peak in % of predicted at the end (mean±SD)	119.61±25.87
Peak power (watt) at baseline (mean±SD)	121.77±48.77
Peak power (watt) at the end (mean±SD)	145.42±60.36
VO2 max in ml/kg/min at baseline (mean±SD)	18.79±5.21
VO2 max in ml/kg/min at the end (mean±SD)	20.67±6.13