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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Cardiac autonomic control during exercise in patients with cardiovascular disease: does it predict prognosis?

Stephanie Meykens
Ine Timmermans

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie in de geestelijke gezondheidszorg

PROMOTOR :

Prof. dr. Dominique HANSEN

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Woord vooraf

Een eindwerk maken is een laatste stap in het behalen van een diploma en tegelijk een eerste stap in de onderzoekswereld. Het is een unieke kans om na vijf jaar studeren je theoretische kennis om te kunnen zetten in een ‘’eigen onderzoek ‘’. Uiteraard gaat dit gepaard met vallen en opstaan en heb je de steun en ervaring van anderen nodig, waarvoor onze oprechte dank.

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Dan rest ons enkel nog u een boeiende, aangename en leerrijke lectuur te wensen.

Paal, 27/06/2018 M.S.

Bilzen, 27/06/2018 T.I.

Research context

This masterscription with the title ‘Cardiac autonomic control during exercise in patients with cardiovascular disease: does it predict prognosis?’ focuses on the rehabilitation of internal conditions, specially cardiovascular disorders, and is drawn up according to the central format by master students in the course ‘Rehabilitation Sciences and Physiotherapy’ at the University of Hasselt. The aim of this duothesis is to investigate if cardiac autonomic control can be improved by cardiac rehabilitation and if this can predict prognosis and life expectancy in patients with cardiovascular disorders (CVD), such as heart failure (HF) and coronary artery disease (CAD).

From 2013, a cardiac rehabilitation programme was started for patients with HF and CAD. The measurements and the programme are performed at the center for rehabilitation and health (ReGo) of the Jessa Hospital. As a result, a large number of patient files are available in the ReGo. Patient data, which are already clinically collected, are used in our research.

For these reasons, both students could immediately start with data acquisition, but first it was discussed with the promoter which parameters had to be extracted. After this, statistical analysis was performed, results were written down in detail and a critical view was given in the discussion section.

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1. Abstract

Background: In patients with cardiovascular disorders (CVD) changes in autonomic function occur, which can lead to sudden death. Cardiac rehabilitation positively affects cardiac autonomic control. However, a connection between an improvement in cardiac autonomic control and prognosis/life expectancy in patients with CVD has not been studied yet. The relation between cardiac autonomic control and prognosis in CVD patients and the impact of rehabilitation, in relation to prognosis, was examined.

Methods: Two hundred patients between age 40 and 75 with diagnosis of congestive heart failure or coronary artery disease underwent a cardiac rehabilitation programme during twelve weeks. The impact of rehabilitation on parameters of cardiac autonomic regulation was investigated, as well as whether an improvement in cardiac autonomic control led to a positive change in prognosis.

Results: Cardiac rehabilitation significantly increased maximal heart rate, reserve heart rate, heart rate recovery in one minute, NN50[1] and pNN50[2]. A significant decrease was achieved in resting heart rate and RMSSD[3]. A significant correlation was found between a change in heart rate reserve (ΔHRreserve) and the number of cardiovascular hospitalisations ($p = 0.0030$; $\rho = -0.1532$). Mean heart rate , RRmean[4], VLF (FFT)%[5], HF (FFT)%[6] and LF (FFT)%[7] were not changed significantly by exercise training.

Conclusion: Cardiac rehabilitation improves cardiac autonomic control and this relates to a lower hospitalisation rate.

Key words: Cardiovascular diseases, cardiac autonomic regulation/control, rehabilitation/exercise training, prognosis/mortality.

[1] The number of adjacent NN intervals that differ from each other by more than 50 ms.
[2] The percentage of adjacent NN intervals that differ from each other by more than 50 ms.
[3] The root mean square of successive differences between normal heartbeats.
[4] The mean of interbeat intervals between all successive heartbeats.
[5] Relative power of the very-low-frequency band (0.0033–0.04 Hz).
[6] Relative power of the high-frequency band (0.15–0.4 Hz).
[7] Relative power of the low-frequency band (0.04–0.15 Hz).

2. Introduction

Cardiovascular diseases (CVD) have become a major global health problem. During the 20th century, changes in population demography, industrial structure, income levels, expenditure patterns, education levels, family structures, eating habits, and physical activity have markedly increased cardiovascular risk factors and disease rates. [1] The leading cause of morbidity and mortality in today's society is CVD, which is responsible for 17,3 million deaths globally each year and it is estimated that this amount will increase up to 23,6 million by the year 2030. [2] CVD comprises many disorders, including heart failure, coronary heart disease, stroke, myocardial infarction and congenital heart disease. The two most common CVDs are heart failure (HF) and coronary heart disease (CHD). [3]

Heart failure (HF) can be defined as "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood." Because of the association with significant mortality, morbidity and healthcare expenditures, HF has been considered as a clinical and public health problem, especially among subjects ≥ 65 years. [4]

Coronary heart disease (CHD) is defined as " a build up of plaque in the arteries of the heart that could lead to heart attack". Patients with high LDL – cholesterol, low HDL – cholesterol, high blood pressure, poor family history, diagnosis of diabetes, history of smoking and elderly age have a higher risk on developing CHD. [5] This disease is a major cause of death and disability and it remains responsible for about one – third or more of all deaths in individuals over age 35. [6,7,8]

The regulation of the heart and the vasculature by the autonomic nervous system plays a key role in enabling the tight coupling between oxygen consumption and delivery. [9] In several cardiac conditions, such as congestive heart failure and myocardial ischemia, alterations in autonomic function occur. An autonomic imbalance, characterized by an elevated sympathetic tone and a lowered parasympathetic tone, is found in various pathological conditions, such as diabetes and acute myocardial infarction. [10] This imbalance has been considered as a final pathway to increased morbidity and mortality. [11] It has been known for decades that sympathetic activation can trigger malignant arrhythmias whereas vagal activity may exert a protective effect. Life – threatening arrhythmias, including ventricular fibrillation and tachycardia, are major causes of sudden death. [12]

Cardiac rehabilitation, mostly consisting of endurance training, has been proven to positively change peak VO_2, flow – mediated dilation, resting systolic and diastolic blood pressure, HDL – cholesterol, resting heart rate, cardiorespiratory fitness and heart rate recovery. [13,14,15] Additional inspiratory muscle training results in a significantly higher benefit in sustained maximal inspiratory pressure, quality of life and dyspnea in congestive heart failure (CHF). [16]

Cardiac rehabilitation also positively effects cardiac autonomic control. Significant improvements in autonomic markers, such as increases in R-R variance, are associated with cardiac rehabilitation. [17] Increases in baroreflex sensitivity (BRS) and the standard deviation of mean R-R interval (RRSD, a measure of heart rate variability) were also found. [18,19] Heart rate recovery at 2 minutes improved with exercise training. [20] Positive effects of cardiac rehabilitation on heart rate variability (HRV) were demonstrated, which revealed the increments in high frequency (HF) and decrements in LF (low frequency)/HF ratio after training. [20] The combination of Tai Chi training and conventional cardiac rehabilitation also led to an improvement in BRS and an increase in the autonomic regulation. [21,22]

CHF remains highly lethal, with better prognosis in women and younger individuals. [23] Patients with CHD also have an abbreviated life expectancy. The majority of the persons succumb to complications of their coronary disease, such as recurrent acute coronary attacks or sudden death. [24] However, a relation between an improvement in cardiac autonomic control and prognosis/life expectancy in patients with cardiovascular disorders has not been studied yet.

The purpose of this study consisted of two parts. First, we examined the effect of cardiac rehabilitation, consisting of endurance training, on parameters of cardiac autonomic regulation (e.g. heart rate variability, heart rate recovery, etc.). Second, we investigated whether an improvement in cardiac autonomic control led to a positive change in prognosis and life expectancy in patients with cardiovascular diseases, mainly heart failure and coronary artery disease. We hypothesize that cardiac rehabilitation will induce an improvement in cardiac autonomic control and that this improvement will positively affect the prognosis and life expectancy in patients with CHF and CAD.

3. Methods

3.1 Design

A retrospective follow – up study on patients with CHF and/or CHD was conducted at the center for rehabilitation and health (ReGO) of the Jessa Hospital, located in Hasselt. A schematic overview of the study design is given in figure 1.

3.2 Participants

Two hundred patients between age 40 and 75 years with diagnosis of CHF and/or CHD were recruited from the Jessa Hospital in Hasselt since 2013, who all underwent a cardiac rehabilitation programme during twelve weeks.

In the Framingham classification, the diagnosis of heart failure is based on the concurrent presence of either two major criteria or one major and two minor criteria. Major criteria include paroxysmal nocturnal dyspnea or orthopnea, neck vein distention, pulmonary rales, radiographic cardiomegaly (increasing heart size on chest radiography), acute pulmonary edema, third heart sound (S3 gallop rhythm), increased central venous pressure (>16 cm H_2O at right atrium), hepatojugular reflux and/or weight loss > 4.5 kg in 5 days in response to treatment. Minor criteria are bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by one third from maximum recorded and/or tachycardia (heart rate > 120 beats/min). [25]

The exclusion criteria were the presence of lung diseases, demention, neurologic disorders and/or oncologic diseases at the beginning of the rehabilitation. Patients who experienced a cardiovascular event during the rehabilitation period, were also excluded from the study. This information was extracted from the medical records of the subjects.

The subjects completed a written informed consent and the study was approved by the Medical Ethics Committee of the Jessa Hospital in Hasselt and the University of Hasselt in Diepenbeek.

3.3 Procedures

At entry of rehabilitation, pulmonary function and cardiopulmonary exercise capacity was assessed by a cardiopulmonary exercise test (CPET). The protocol that was being used, is described in a study of Hansen et al. [28] A maximal exercise test to volitional exhaustion on a cycle ergometer was executed. Based on sex and age, a starting and incremental load between 10 and 40 W is selected. Patients had to maintain a cycling frequency of 60 – 70 rpm. Peak oxygen uptake (VO_{2peak}) and respiratory exchange ratio (RER) were collected every ten seconds by continuous pulmonary gas exchange analysis. Heart rate was also monitored every ten seconds using a 12 – lead electrocardiographic device. When the patient was not able to maintain a cycling frequency of at least 60 rpm, the test was ended. During the test, the patients were encouraged to reach a maximal exercise test, based on RER $\geq$ 1.1. Subjective parameters, such as fatigue, dyspnea and leg muscle pain, were also used by an experienced tester to confirm if a maximal test was performed. The first and second ventilatory thresholds (VT1, VT2) were calculated using the V – slope and the VE/VCO2 slope.

Heart rate (HR) was monitored continuously during the test using a 12-lead electrocardiogram. Resting HR was assessed while sitting on bike for 1 minute, from which the lowest recorded HR was considered as resting HR. [29] Maximum HR and heart rate recovery in one minute (HRR 1') were also evaluated. HRR was assessed while cycling at 30W during two minutes. These parameters were used to determine the patient's heart rate reserve (HRR). RR-intervals were measured during the first minute of the test. Based on these intervals, the following parameters were extracted: RRmean, HRmean, RMSSD, NN50 and pNN50 as time – domain results and the percentage of the FFT spectrum [VLF (%), LF (%) and HF (%)] as frequency-domain results.

These parameters are measures of heart rate variability (HRV). RMSSD is the root mean square of successive differences between normal heartbeats and is the primary time – domain measure used to estimate the vagally mediated changes reflected in HRV. [30] It reflects the integrity of vagus nerve – mediated autonomic control of the heart. [31] NN50 is the number of adjacent NN intervals that differ from each other by more than 50ms and pNN50 is the percentage of this number. [30] The pNN50 is closely correlated with activity of parasympathetic nervous system (PNS). [32] It is correlated with the RMSSD and HF power. [33]

VLF (%) is the relative power of the very – low – frequency band (0.0033 – 0.04Hz). [30] The VLF rhythm is affected by the heart's intrinsic system as the sympathetic nervous system (SNS) influences the amplitude and frequency of its oscillations. [34] VLF power is strongly associated with all – cause mortality [35-38] and affected by PNS activity since parasympathetic blockade almost completely abolishes it. [39] LF (%) is the relative power of the low – frequency band (0.04 – 0.15Hz). [30] LF power may be produced by both the PNS and SNS, and blood pressure regulation via baroreceptors. [40] During resting conditions, the

LF band reflects baroreflex activity and not cardiac sympathetic innervation. [34] HF (%) is the relative power of the high – frequency or respiratory band (0.15–0.40 Hz). The HF band reflects PNS activity and is called the respiratory band, because it corresponds to the variations in heart rate related to the respiratory cycle. [30] HF power is high correlated with the time – domain measures pNN50 and RMSSD. [41]

A schematic overview of the measured parameters is given in Fig 2.

After the CPET, the patients underwent a rehabilitation programme during twelve weeks at the Center of Rehabilitation and Health (ReGo) in the Jessa Hospital. The programme included three sessions per week with 45 minutes per session. Each session consisted of aerobic training on a treadmill, a cycle ergometer and an ergometer. Patients were instructed to train at a moderate intensity, between VT1 and VT2.

3.4 Outcome measures

Cardiac autonomic regulation was considered as the primary endpoint of this study. HRrest, HRmax, HRR, HRV and heart rate recovery provided an accurate image of the cardiac autonomic regulation during exercise as mentioned earlier.

In addition to the primary endpoints, other parameters are also displayed. The cardiovascular (CV) risk profile was also further examined. Parameters, as blood pressure (BP), lipid profile, weight and body mass index (BMI), were observed. Blood pressure (BP) was measured in rest and every 3 minutes during the CPET and the recovery phase with a blood pressure cuff. After an overnight fast, subjects reported at the laboratory. Blood samples were analyzed total cholesterol (TC) and low – density lipoprotein (LDL). Weight and BMI were measured using a calibrated analog weight scale.

The relationship between cardiac autonomic regulation and prognosis was also studied. Mortality, hospitalisation rate and the occurrence of major adverse cardiac events (MACE) were used as outcome measures for prognosis during two years after the rehabilitation programme. Mortality had to be related to a cardiovascular cause. Only hospitalisations for cardiovascular reasons were included in this study. The number of hospitalisation days was also examined. Finally, it was checked whether the patients underwent one of more MACE (s) during the follow – up period. Restenosis, recurrent angina pectoris, cardiac arrhythmias and myocardial infarction were seen as a MACE.

3.5 Statistics

The obtained data were processed using the statistical program JMP. The statistical analysis consisted of three parts.

In the first part, we analyzed if rehabilitation had a significant impact on the following parameters: HRmax, HRrest, HRreserve, HRR 1', HF (FFT)%, LF (FFT)%, VLF (FFT)%, HRmean, RRmean, NN50, pNN50 and RMSSD. At baseline, analyses of normality (Shapiro – Wilk) and homoscedasticity (O' Brien, Brown - Forsythe, Levene, Bartlett) were performed to evaluate

if the participants in the group were comparable. If the data were normally distributed the 2 – tailed t – test was performed at 12 weeks to compare patients at pre – measurements and post – measurements. If the data were not normally distributed, the two – tailed Wilcoxon sign rank was performed for the same purpose. We also checked if covariates (change in beta – blocker dose and ΔRERpeak) had an effect on those parameters. The parameters, on which rehabilitation had a significant effect ($p < 0.05$, two – tailed) were used in part two of the statistical analysis.

In the second part, we investigated the possible correlations ($p < 0.05$, two – tailed) between the parameters, on which rehabilitation had a significant effect, and the following continuous X – variables: Change in systolic blood pressure (ΔSBP), in diastolic blood pressure (ΔDBP), in peak oxygen uptake (ΔVO2peak), in total cholesterol (ΔTC), in low – density cholesterol (ΔLDL), in weight (ΔWeight) and in body mass index (ΔBMI). First, it was checked whether the data were normally distributed. If this was the case, univariate regression (Pearson correlation) was performed. When normality was not met, the Spearman correlation was used. Possible correlations between the parameters of part one and three categorical variables – gender, condition (HF/CAD) and smoking behaviour – were also considered.

During the last part, we checked whether significant improvements ($p < 0.05$, two – tailed) in cardiac autonomic regulation led to a positive impact on the prognosis of the patients. This included mortality, number of hospitalisation (days) and the occurrence of major adverse cardiac events (MACE), like recurrent angina pectoris, acute myocardial infarction, cardiac arrhythmias and restenosis. For the analysis of mortality and MACE, log-linear models were used and for hospitalisations multivariate regression. If the data were not normally distributed, the nonparametric alternative was used. Because the duration of the follow – up could vary from patient to patient, the number of follow – up days was included as a predictor in all three statistical models.

4. Results

4.1 Study population

Two hundred patients (aged, 63 ± 10.10 years, 19% women, 37.5% HF) were enrolled in this study. Physical, clinical and other characteristics are shown in Table 1. All patients started a twelve week cardiac rehabilitation programme in the Jessa Hospital in Hasselt. A flowchart of the trial is presented in Fig. 3. Of the two hundred patients who began the study, seven withdrew prematurely. Most common reasons for drop-out were AMI, PTCA, other surgical procedure and unknown reasons.

4.2 Impact of revalidation on cardiac autonomic control

As shown in table 2 and Fig. 4, cardiac rehabilitation had a significant effect on seven out of twelve parameters. Maximal heart rate, heart rate reserve, heart rate recovery in one minute, NN50 and pNN50 increased significantly ($p < 0.0001$; $p < 0.0001$; $p < 0.0001$; $p = 0.0090$ and $p = 0.0026$). A significant decrease was achieved in resting heart rate and RMSSD ($p = 0.0009$ and $p = 0.0065$). HRmean, RRmean, VLF (FFT)%, HF (FFT)% and LF (FFT)% were not changed significantly by exercise training ($p = 0.2315$; $p = 0.2376$; $p = 0.3386$; $p = 0.4232$ and $p = 0.8161$).

Since the beta – blocker dose was adjusted in a number of patients (n = 61, 31.60%) during the programme, it was also examined whether this adjustment could have an effect on the change in the parameters above. The RERpeak was also included in this analysis, since not all patients reached their maximal capacity during the CPET (RERpeak < 1.1). Increasing the dose had a significant effect on maximal heart rate, resting heart rate and mean heart rate ($p = 0.0010$; $p = 0.0032$ and $p = 0.0012$). Maximal heart rate, resting heart rate, HF (FFT)% and mean heart rate were significantly changed by dose reduction ($p < 0.0001$; $p < 0.0001$; $p = 0.0162$ and $p < 0.0001$). The change in RERpeak only had a significant effect on mean heart rate ($p = 0.0362$).

4.3 Correlations

Significant positive correlations were found between ΔHRmax, ΔHRreserve and ΔHRR 1' on the one hand and ΔVO2peak on the other ($p < 0.0001$; $p < 0.0001$ and $p = 0.0001$). ΔWeight also negatively correlated with ΔNN50, ΔpNN50 and ΔRMSSD ($p = 0.0355$; $p = 0.0064$ and $p = 0.0235$). This significant negative correlation was also found between ΔBMI, ΔpNN50 and ΔRMSSD ($p = 0.0312$ and $p = 0.0258$). Having heart failure had a significant negative impact on ΔHRmax and ΔHRreserve ($p = 0.0420$ and $p = 0.0126$). A significant positive correlation was demonstrated between male gender and ΔpNN50 ($p = 0.0258$). An overview of the p – values, correlation coefficients and F – ratios are given in Table 3.

4.4 Relation to prognosis

Two patients (1.04%) died of a non – cardiac cause during the follow – up period of two years. Forty-five out of 193 patients (23.32%) were admitted to the hospital for cardiovascular reasons during these two years. The largest number of hospitalisations was seven (mean 0.44) and hospitalisation days ranged from zero to fifty (mean 1.47). Twenty – nine patients underwent one of more major adverse cardiac event(s): Recurrent angina pectoris (n = 9), restenosis (n = 8), cardiac arrhythmias (n = 19) and myocardial infarction (n = 5).

As shown in Table 4, a significant correlation was found between ΔHRreserve and the number of cardiovascular hospitalisations ($p = 0.0330$; $\rho = -0.1532$). Significant changes in HRmax, HRreserve, HRrest, HRR 1', NN50, pNN50 and RMSSD, induced by cardiac rehabilitation, did not lead to significant changes in prognosis.

5. Discussion

Cardiac rehabilitation improves cardiac autonomic control and this relates to a lower hospitalisation rate.

The positive effect of a cardiac rehabilitation programme on autonomic control of the heart is supported by the increase in time – domain measures of HRV, HRmax, HRreserve, HRrest and HRR during one minute. Heart rate variability is a noninvasive, practical and reproducible measure of autonomic nervous system function. A variable heart rate that is responsive to demands, is believed to bestow a survival advantage, whereas there is an association between reduced HRV and poorer cardiovascular health and outcomes. [42]

As in previous studies [17,19,43], we observed an improvement in HRV after exercise training. For instance, Lucini et al.[17] reported that exercise – based rehabilitation led to a significantly increased RR – interval, RR – variance and an overall gain of arterial pressure/heart period baroreflex (7.44 +/- 1.20 ms/mm Hg to 12.12 +/- 1.48 ms/mm Hg, $p < 0.001$) in CAD patients. The findings of the review of Routlegde et al. [19] suggested that exercise therapy may improve HRV in myocardial infarction, chronic heart failure and revascularization patients by increasing vagal tone and decreasing SNS activity. Oliveira et al. [43] concluded that eight weeks of exercise – based cardiac rehabilitation was an insufficient stimulus to improve cardiac autonomic function in post – myocardial patients. The systematic review of Chung-Yin et al. [44] demonstrated positive effects of exercise training on HRV which revealed the increments in high frequency and decrements in low frequency/high frequency ratio after training in patients with chronic heart failure. This study revealed significant improvements in the HRV time – domain measures NN50, pNN50 and RMSSD. These parameters reflect overall autonomic modulation with parasympathetic components.

Besides HRV, we also investigated the effect of cardiac rehabilitation on heart rate recovery during one minute (HRR 1') after effort. HRR 1' is considered a marker of cardiac parasympathetic outflow. [45] The ability of heart rate to recover after exercise is related to the capacity of the cardiovascular system mediated by vagal activity and baroreceptor adaptations that occur during effort. [46] For this reason, HRR can be an additional indicator of risk stratification and outcome measures in patients undergoing cardiac rehabilitation. [47] A previous study [43] showed that moderate – intensity aerobic exercise training was effective in improving HRR, especially during two minutes.

This study also demonstrated significant improvements in maximal heart rate, resting heart rate and heart rate reserve. Chung-Yin et al. [44] explained that an increase in vagal tone after training is implied by the reduction in resting heart rate and that an increase in peak heart rate suggests enhanced sympathetic drive, lowered vagal influence or both at peak exertion during effort. Several studies have reported that changes in HRR were attributed to a greater heart rate reserve after exercise training [47,48], but they do not negate the potential influence of training on autonomic balance. Our results and those of the previous

studies mentioned indicated that cardiac rehabilitation provided a benefit to cardiac autonomic control.

Important to keep in mind is that cardiac rehabilitation is a multifunctional risk factor prevention programme that includes dietary and educational interventions with emphasis on various psychological factors and stress management. [49,50] The role of these various factors of the cardiac rehabilitation programme were not addressed separately in this study, but it is quite possible that the stress management component may have contributed to the favourable results that we have described, because mental stress can reduce baroreflex gain. [51]

Assumingly, this is the first study to investigate the relation between an improvement in cardiac autonomic control and prognosis in patients with cardiovascular diseases. A significant correlation was shown between the change in heart rate reserve, induced by cardiac rehabilitation, and the number of hospitalisations for cardiovascular reasons. The clinical messages of the present study are that (1) a cardiac rehabilitation programme was shown to be adequate to improve cardiac autonomic control and that (2) an increase in heart rate reserve, induced by physical activity, is related to a decrease in the cardiovascular hospitalisation rate.

Study limitations need to be emphasized. The collection of the RR – intervals happened manually, because no polar was used during effort. This is, of course, a much less accurate way of data collection. Due to the time – consuming nature of the data collection, we were able to determine RR – intervals for only 1 minute of effort. A previous study of Shaffer et al. [30] showed that the VLF band requires a recording period of a least five minutes, the LF band a minimum of 2 minutes and the HF band a minimum one minute period. NN50 and pNN50 also require a two minute epoch. While the conventional minimum recording for RMSSD is 5 minutes, researchers have proposed ultra – short – term periods of ten, thirty and sixty seconds. The length of the recording period significantly affects both HRV time – domain and frequency – domain results [30]. For this reason, our short recording length may have a possible effect on the HRV measurements.

This research also has a number of strengths. First, a relatively big sample size (n = 200) with only 7 drop –outs during the rehabilitation programme. Secondly, this is the first study to assess the impact of short – term improvements in cardiac autonomic control on prognosis in patients with CAD and HF. Many previous studies [42,43,44] examined the effect of exercise training on autonomic function, but a link to long – term prognosis was never investigated.

Further research could examine the additional effects of other components of cardiac rehabilitation, such as stress management and dietary intake. Another implication is research concerning high – intensity interval aerobic training of resistance training. These

modalities may also influence the obtained effects, because a threshold intensity or amount of exercise may be needed to affect cardiac autonomic function. [44]

6. Conclusion

According to this retrospective follow – up study, cardiac autonomic control has a positive effect on the cardiac autonomic control in patients with cardiovascular diseases. A significant correlation was found between a change in heart rate reserve and the number of cardiovascular hospitalisations. In conclusion, physical activity improves cardiac autonomic function and this relates to a lower hospitalisation rate.

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8. Appendices

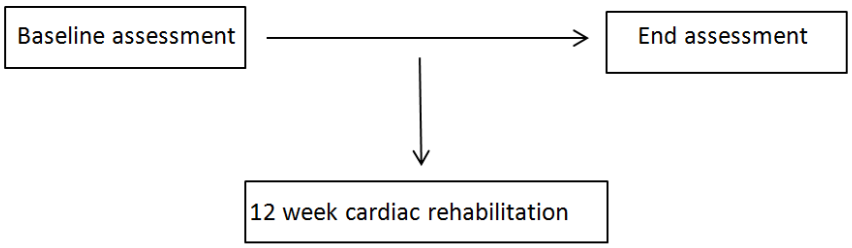

Fig 1. Study design

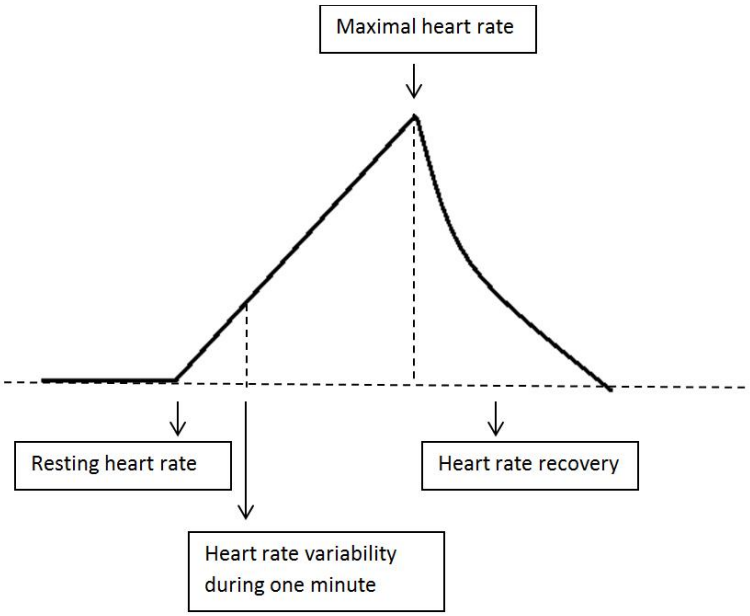

Fig 2. Primary outcome measures

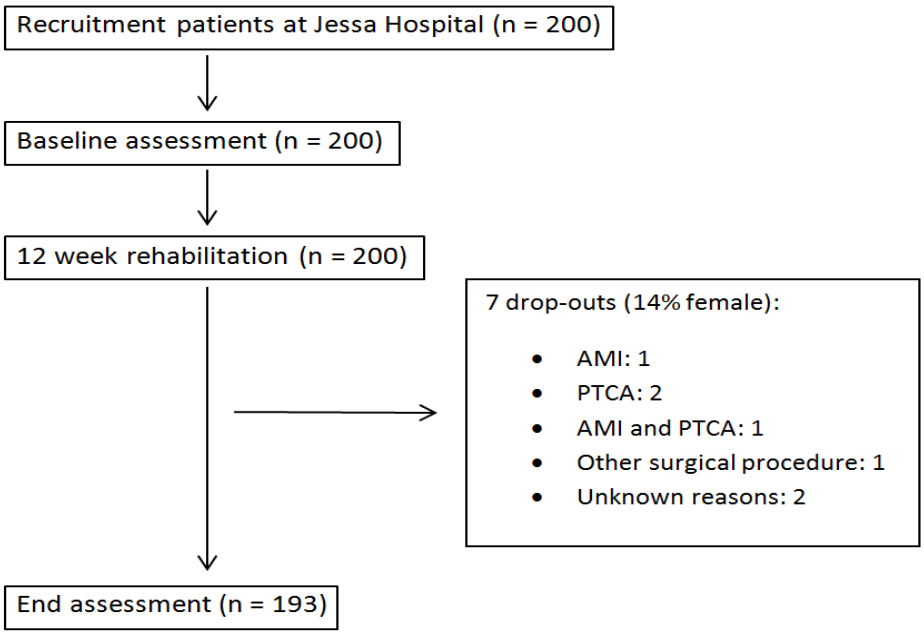

Fig 3. Flowchart

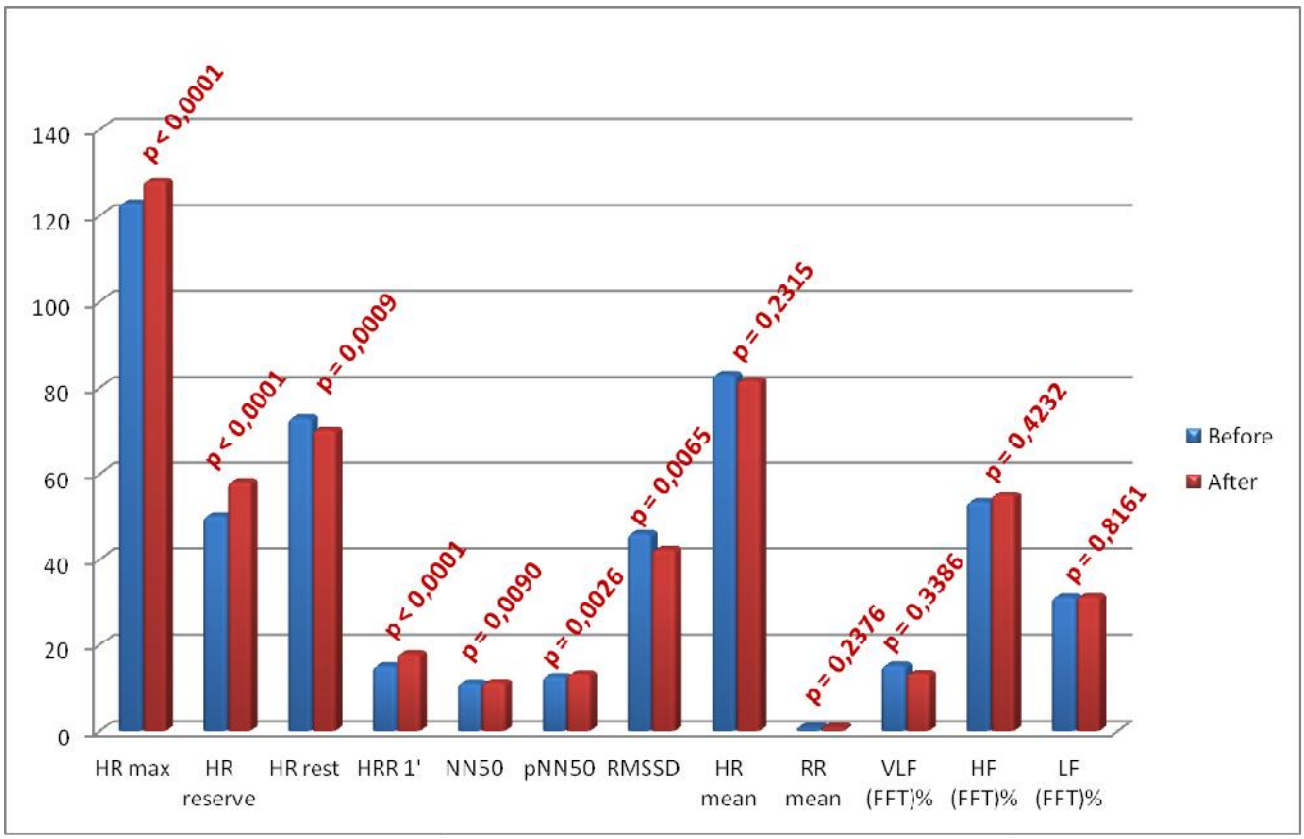

Fig 4. Graphic display of change in cardiac autonomic control

Table 1. Characteristics of study population

Physical characteristics *	
Sex **	
Male	162
Female	38
Age, y	63 ± 10.10
Weight, kg	81.59 ± 15.83
Height, cm	172.37 ± 8.99
BMI, kg/m²	27.21 ± 4.72
Clinical characteristics **	
CAD	125
HF	75
Co morbidities **	
Diabetes	35
Hypertension	99
Cardiovascular profile*	
Lipid profile	
Total cholesterol, mg/dl	177.36 ± 43.75
LDL, mg/dl	100.19 ± 36.46
Blood pressure	
Systolic BP, mmHg	140 ± 21.10
Diastolic BP, mmHg	79 ± 11.88
Medication **	
ACE inhibitors	82
Statins	161
Beta – blockers	157

** Data are presented as mean ± SD*

*** Data are presented as number of subjects*

Table 2. Changes in parameters for cardiac autonomic control

Parameters	Before	After	p-value
HRmax	122.9 +/- 24.08	128.0 +/- 24.28	< 0.0001*
HRreserve	50.03 +/- 21.53	58 +/- 22.41	< 0.0001*
HRrest	72.84 +/- 13.84	70.03 +/- 12.28	0.0009*
HRR 1’	15.16 +/- 8.63	17.90 +/- 9.76	< 0.0001*
NN50	11.11 +/- 14.88	11.24 +/- 10.60	0.0090*
pNN50	12.72 +/- 16.51	13.34 +/- 12.45	0.0026 *
RMSSD	45.85 +/- 47.99	42.22 +/- 32.71	0.0065 *
HRmean	82.97 +/- 14.32	81.62 +/- 12.73	0.2315
RRmean	0.745 +/- 0.12	0.76 +/- 0.12	0.2376
VLF (FFT)%	15.30 +/- 15.59	13.45 +/- 13.19	0.3386
HF (FFT)%	53.42 +/- 22.13	54.93 +/- 18.44	0.4232
LF (FFT)%	31.29 +/- 16.29	31.32 +/- 14.64	0.8161

Data are presented as mean ± SD

HR = Heart rate, HRR = Heart rate recovery

** p < 0.05 (Significant)*

Table 3. Correlations

Parameter		ΔSBP	ΔDBP	ΔVO2peak	ΔTC	ΔLDL	ΔWeight	ΔBMI	Age
ΔHRmax	p - value	0.4079	0.6666	< 0.0001*	0.8149	0.1676	0.8622	0.9031	0.2595
	ρ	- 0.0816	- 0.0355	0.4241	-0.0178	- 0.1060	0.0128	0.0091	- 0.0816
ΔHRreserve	p - value	0.5426	0.2825	< 0.0001*	0.4825	0.1327	0.2632	0.6175	0.4889
	ρ	0.0503	- 0.0883	0.5595	- 0.0534	- 0.1154	- 0.0825	- 0.0375	- 0.0501
ΔHRrest	p - value	0.7893	0.3310	0.1553	0.6917	0.9431	0.2161	0.5235	0.7493
	ρ	0.0221	0.0799	- 0.1035	0.0302	- 0.0055	0.0911	0.0479	- 0.0232
ΔHRR 1’	p - value	0.5136	0.5834	0.0001*	0.5601	0.3010	0.0622	0.2167	0.0897
	ρ	0.0539	- 0.0451	0.2761	- 0.0433	- 0.0795	- 0.1370	- 0.0925	0.1255
ΔNN50	p - value	0.9499	0.1273	0.8995	0.8545	0.7843	0.0335*	0.0927	0.3889
	ρ	0.0052	- 0.1251	0.0092	- 0.0140	- 0.0211	- 0.1560	- 0.1257	0.0624
ΔpNN50	p - value	0.8835	0.1108	0.8737	0.9386	0.8421	0.0064*	0.0312*	0.1342
	ρ	0.0121	- 0.1307	- 0.0116	- 0.0059	- 0.0153	- 0.1994	- 0.1606	0.1082
ΔRMSSD	p - value	0.9051	0.3109	0.5897	0.8724	0.9721	0.0235*	0.0258*	0.3517
	ρ	- 0.0099	- 0.0833	- 0.0394	- 0.0122	- 0.0027	- 0.1661	- 0.1662	0.0674

Parameter		Gender	Condition (HF/CAD)	Smoking behaviour
ΔHRmax	p - value	0.6378	0.0420*	0.1453
	F – ratio	0.2223	4.1923	1.9491
ΔHRreserve	p - value	0.8772	0.0126*	0.0823
	F – ratio	0.0239	6.3499	2.5310
ΔHRrest	p - value	0.4306	0.8164	0.2310
	F – ratio	0.6238	0.0541	1.4769
ΔHRR 1’	p - value	0.3493	0.2125	0.0812
	F – ratio	0.8803	1.5647	2.5452
ΔNN50	p - value	0.0573	0.3947	0.3966
	F – ratio	3.6588	0.7279	0.9295
ΔpNN50	p - value	0.0258*	0.5008	0.1639
	F – ratio	5.0503	0.4550	1.8259
ΔRMSSD	p - value	0.1360	0.2569	0.4501

	F – ratio	2.2423	1.2932	0.8016

Data are presented as p – value/correlation coefficient ρ or F – ratio

HR = Heart rate, HRR = Heart rate recovery

** p < 0.05 (Significant)*

Table 4. Impact of change in parameters on prognosis

Prognostic parameter		**ΔHRmax**	**ΔHRreserve**	**ΔHRrest**	**ΔHRR 1'**	**ΔNN50**	**ΔpNN50**	**ΔRMSSD**
Mortality	p - value	0.3608	0.7768	0.4130	0.9175	0.8449	0.7208	0.8254
	L-R ChiSquare	0.83520409	0.29585157	0.67014983	0.01073318	0.03828379	0.12770286	0.04864841
Number of hospitalisations	p - value	0.4099	0.0575	0.2844	0.1785	0.9248	0.9068	0.6064
	ρ	- 0.0597	- 0.1370	0.0774	- 0.0973	- 0.0068	- 0.0085	0.0373
Number of hospitalisation days	p - value	0.3466	0.0330*	0.2292	0.1673	0.9218	0.8776	0.5506
	ρ	- 0.0681	- 0.1532	0.0869	- 0.0998	- 0.0071	- 0.0112	0.0432
MACE	p - value	0.5272	0.0953	0.4150	0.2127	0.8947	0.9425	0.2484
	L-R ChiSquare	3.18596615	7.90000122	3.93389304	5.82412612	1.09712842	0.76967433	5.40272176
Specific MACE combination	p - value	0.6765	0.1189	0.6856	0.4975	0.7673	0.7801	0.5956
	L-R ChiSquare	5.73846057	12.8016399	5.65704186	7.36752615	4.90892118	4.78641422	6.46186344

Data are presented as p – value/ L-R ChiSquare

HR = Heart rate, HRR = Heart rate recover, MACE = Major adverse cardiac event

** p < 0.05 (Significant)*

Table 5. Progress form master thesis part two

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KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
27/09	Start Masterproef Deel 2	Promotor: Copromotor: Student(e): [illegible] Student(e):
4/10	Rondleiding ReGio Hasselt + bijhorende uitleg omtrent testen en toestellen	Promotor: Copromotor: Student(e): [illegible] Student(e):
25/01	Overlopen van data-analyse	Promotor: Copromotor: Student(e): [illegible] Student(e):
07/03	starten van statistiek	Promotor: Copromotor: Student(e): [illegible] Student(e):
13/04	statistiek omtrent prognose verder uitdiepen	Promotor: Copromotor: Student(e): [illegible] Student(e):
31/05	Overlopen volledige masterproef	Promotor: Copromotor: Student(e): [illegible] Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):

Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
Cardiac autonomic control during exercise in patients with cardiovascular disease: does it predict prognosis?

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie in de geestelijke gezondheidszorg**
Jaar: **2018**

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