KU LEUVEN

GROEP BIOMEDISCHE WETENSCHAPPEN

FACULTEIT BEWEGINGS- EN REVALIDATIEWETENSCHAPPEN

Resting heart rate in permanent atrial fibrillation: predictive for trainability?

door Christophe Mortelmans

masterproef aangeboden tot het behalen van de graad van Master of Medicine in de sportgeneeskunde

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dr. K. Goetschalckx, promotor

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WOORD VOORAF

Graag wil ik mijn oprechte dank betuigen aan dr. Kaatje Goetschalckx, mijn promotor, voor haar vakkundige en aangename begeleiding van deze masterproef sportgeneeskunde. Van meet af aan heb ik haar ervaren als een gemotiveerde en hartelijke experte, die met oprechte betrokkenheid haar promovendi van advies wenste te voorzien.

Graag wil ik ook mijn dankbaarheid uiten jegens mijnheer Dirk Schepers, database-kenner en revalidatiekinesist, voor de namiddagen waarop we ons samen in de statistiek verdiepten. Geen vraag was hem daarbij te veel en dat heb ik zeer geapprecieerd.

Tot slot wil ik nog graag het hele team van de afdeling cardiale revalidatie van het U.Z. Leuven bedanken, voor de stage die ik er kon lopen op functiemetingen en op revalidatietraining. Het heeft tot een beter begrip geleid van de materie die in mijn onderwerp aan bod komt.

Ik zie het aanbieden van deze masterproef als een mooie afsluiter van negen jaar studie aan de KU Leuven, waar ik – dankzij mijn ouders – de opleidingen huisarts- en sportgeneeskunde mocht genieten. Ik ervaar dit afstuderen tevens als een oproep tot verdere verfijning van de klinische en wetenschappelijke kennis als alumnus en het omzetten van het aangeleerde in de praktijk.

Mechelen, 14 mei 2016 C.M.

SITUERING

Deze masterproef kadert in de opleiding sportgeneeskunde, een samenwerking tussen de faculteit bewegings- en revalidatiewetenschappen en de faculteit geneeskunde aan de KU Leuven. Mijn promotor, dokter K. Goetschalckx, is als cardiologe verbonden aan het U.Z. Leuven.

De onderzochte populatie in deze masterproef betreft hartpatiënten die lijden aan een aanhoudende vorm van voorkamerfibrillatie ("VKF"). Dat is een frequente hartritmestoornis die kan leiden tot verminderde inspanningsmogelijkheden. In onze studie wilden we evalueren of deze patiënten baat zouden kunnen hebben bij het volgen van een fysiek trainingsschema voor hartpatiënten: een cardiaal revalidatieprogramma. Het opstellen van adequate trainingsschema's voor deze patiënten is vaak moeilijk. Zo'n plan wordt namelijk ontwikkeld o.b.v. hartslag-trainingszones. Dat is echter een grotere uitdaging wanneer de hartslagfrequentie onregelmatig en hoger dan gemiddeld is, zoals bij dit ritmeprobleem. We waren ook geïnteresseerd in een mogelijk verschil in uitkomst tussen patiënten met een initieel hogere of lagere hartslagfrequentie in rust. Mogelijks zouden patiënten die al bij aanvang een hoge rusthartslag hebben, bij inspanning sneller aan hun maximum zitten en dus minder goed kunnen presteren. Hun hart kan immers niet meer voldoende zuurstof naar het lichaam pompen eens het niet meer kan versnellen. Bij mensen zonder ritmestoornis zien we n.a.v. zo'n oefenprogramma doorgaans o.a. een daling van de rusthartslag en een toename van de maximale inspanningscapaciteit. Er is nog niet veel onderzoek gebeurd naar deze relaties specifiek in patiënten met deze ritmestoornis. Het is niet ondenkbaar dat de patiënten bij wie de rusthartslag moeilijker 'gekalmeerd' kan worden tot een lagere frequentie, ook minder winst zouden kunnen boeken door fysieke training en dus minder "trainbaar" zijn. Zo stelde zich de vraag of conditieverbetering door training in verband staat met met de rusthartfrequentie bij patiënten in aanhoudende VKF.

Om dit alles goed te kunnen meten en oplijsten werd beroep gedaan op de kennis en kunde van de afdeling cardiale revalidatie van het U.Z. Leuven. Zij stonden onder meer in voor de begeleiding van de trainingssessies en voor het afnemen van de maximale fietsproeven. Zo'n inspanningstest op de fiets is nodig om een aantal parameters te bepalen om een uitspraak te kunnen doen over de (evolutie in) hartslag en inspanningsvermogen.

Resting heart rate in permanent atrial fibrillation: predictive for trainability?

Abstract

Background: Atrial fibrillation (AF) is a common arrhythmia that can lead to lower exercise capacity. In our retrospective study, we wanted to confirm the effect of cardiac rehabilitation on peak oxygen consumption in permanent AF patients. Furthermore, we wanted to investigate if exercise performance was correlated with resting heart rate in this population.

Methods and results: Cardiac patients, who were referred for rehabilitation training, performed a maximal exercise test at baseline and after three months of the exercise program. Patients in permanent AF (n = 63) were dichotomized according to the median initial resting heart rate (81 bpm). Peak VO_2 and its evolution did not differ between the lower and the higher resting heart rate group. In all, a 21% increase in peak VO_2 and a 3bpm decrease in resting heart rate were noted. The mean percentage of predicted VO_2 was 68 at baseline and increased to 81. The mean chronotropic competence increased by 10 bpm in total and by 21bpm in the higher resting heart rate group.

Conclusion: Our study results in permanent AF patients confirm a prominent increase in exercise capacity after a three month exercise training program, without adverse events. Resting heart rate was not correlated with trainability. Patients with a higher resting HR at baseline did not make less progress. These findings favor a less stringent pharmacological rate control policy, in combination with encouragements to engage in exercise therapy. Further research is needed to optimize the balance between the pharmacological and physiological heart rate lowering treatment by exercise training.

Keywords

Resting heart rate, permanent atrial fibrillation, exercise capacity, cardiac rehabilitation

Background

Atrial fibrillation

Affecting more than 8.8 million adults in the European Union, atrial fibrillation (AF) is currently the most common sustained cardiac arrhythmia[1]. The prevalence of AF is about 2.2% and increases with age: rising to 6.4% in people aged 60 and older to over 8% in a population aged 80 and older[1-2]. The prevalence of AF is estimated to at least double by 2050[3-4], which will drastically influence associated medical costs[5-7]. The presence of AF can lead to serious complications. Both paroxysmal and permanent AF double mortality and triple the chance of developing congestive heart failure[8]. Atrial fibrillation also increases the risk of stroke with a factor five[9-10]. Over 20% of all cerebrovascular accidents (CVA) are directly attributable to AF[3-4]. An effective antithrombotic therapy is indispensable and reduces the risk of stroke with 60%[11]. Furthermore, AF has showed a reduction in exercise tolerance of 15-20%[12-14], accounting for an important decrease in quality-of-life. Rate and rhythm control result in an equal prognosis[15-16]. In search of the possible recovery of exercise capacity however, rhythm control is the first therapeutic goal[17]. After failure of cardioversion to sinus rhythm or when AF is allowed to continue, a large group of patients end up in permanent atrial fibrillation[18]. In this group, rate control is the best treatment option[19].

Heart rate at rest and exercise capacity in permanent atrial fibrillation

To describe exercise capacity, mainly peak oxygen uptake (VO_2) is used[20-21]. In daily practice, resting heart rate (HR) is a substitute clinical parameter that is easier to obtain. The correlation between HR at rest and exercise capacity[22-25] is well documented in the general population[26-28] as well as in patients with cardiovascular disease[20-21,29-30]. In general, lower resting HR values were associated with better fitness levels and more favourable outcomes[22-25]. Less data are available concerning this relation when focussing on patients with atrial fibrillation. The lower exercise capacity in AF patients is mainly explained by an irregular, often rapid ventricular response at rest and during exercise, which limits cardiac output[31]. Even though rate control is an important part of accepted treatment of permanent atrial fibrillation, recent literature does not show better peak-VO_2 in AF patients with lower HRs[32-34]. On the contrary, a recent study by Kato et al.[35] showed a weak positive correlation between resting HR and percentage of predicted peak oxygen consumption. These findings suggest a different contribution of resting HR to exercise capacity, depending on the rhythm status of the patient.

Exercise training in permanent atrial fibrillation.

Exercise training is an important, integrated part of the prevention and treatment of different forms of cardiac morbidity[36]. Few studies were conducted to investigate the effect of exercise training in

subjects with permanent atrial fibrillation. Mertens et al.[37] mention this could be due to an aversion of training patients with a chronic arrhythmia and the difficulty to fix training program intensity zones based on an irregular HR. A systematic review by Reed et al.[38] suggests that exercise training can play a promising role in the management of permanent atrial fibrillation. Another meta-analysis by Giacomantonio et al.[39], describing the health benefits of physical activity among individuals with AF, also found positive results regarding improvement of exercise capacity and quality of life.

Research question

The goal of this retrospective study was to further investigate the relationship between exercise capacity and resting HR or change in resting HR, after training of permanent AF patients. Moreover, we sought to clarify any differences between a high- and a low resting HR group (H-HR and L-HR respectively). We hypothesized that patients with higher resting HR might have a more modest training potential, expressed by a smaller increase in peak-VO_2 and a smaller reduction of HR at rest or during exercise. Furthermore, this investigation created the opportunity, based on our own data, to confirm the previous conclusion[38-40] that exercise training is beneficial for exercise capacity (using peak-VO_2) in permanent AF.

Methods

Study population and data collection

A database was available of all cardiac patients (n = 2203) who were referred to the ambulatory cardiac rehabilitation program of the University Hospitals of Leuven between 2010 and 2015. In this database, all patients with permanent atrial fibrillation were selected for further analysis. Patients' characteristics were noted from medical records, such as age, gender, height, weight, New York Heart Association (NYHA) classification, cardiovascular risk factors and disease, reason for referral, medication with an anti-hypertensive, anti-arrhythmic or anticoagulant goal. Patients with a known history of chronic AF were excluded when they were not in AF at one or both measurement moments of the study. We divided the patients into a H-HR and a L-HR group according to a resting heart rate higher or lower than the median HR on the initial 12-lead ECG at rest. Both groups were offered the same exercise tests and cardiac rehabilitation program. All participants signed a written informed consent. The study was approved by the ethical review board of the Medical Faculty of the KU Leuven, Belgium (no MP 10324).

Exercise training

Patients took part in an ambulatory, supervised exercise training program[40] for a period of 3 months. Three exercise sessions per week were offered with a duration of approximately 90 minutes per

session. Each session consisted of cycling, running, arm ergometry, rowing, predominately isotonic calisthenics and relaxation. Exercise intensity was determined individually for each patient separately by calculating an interval for training HR (training HR = resting HR + 60%-90% [peak HR-resting HR]).

Cardiopulmonary exercise testing (CPET): cyclo-ergometry

All patients were to perform two maximum incremental exercise tests: one at baseline and another – when compliant – after finishing a rehabilitation program of three months. Both tests were performed on an upright cycle ergometer (Oxycon Pro, Jaeger, CareFusion, Germany)[41] in controlled laboratory conditions and under supervision of an expert. A 12-lead electrocardiogram was taken at rest. The initial workload of 20W was increased by 20W every minute until exhaustion. Blood pressure was measured every minute. Both ECG and respiratory data were monitored continuously during the test. HR was calculated from the electrocardiogram. The gas analyzers and the flowmeter were calibrated before each study according to the manufacturer's instructions. Oxygen uptake (VO_2) and carbon dioxide output (VCO_2) were determined from the measurement of oxygen and carbon dioxide concentration in the inspired and expired air. The maximum VO_2 value during the last fully finished bout of 30 seconds was taken as peak VO_2. Individual peak VO_2 results were compared with predicted reference values of Wasserman et al.[42] to determine percentage of predicted peak VO_2. The respiratory gas exchange ratio (RER: VCO_2/ VO_2), was calculated. Patients who performed a submaximal exercise test, evidenced by a peak RER < 1.1[41], were excluded from further analysis.

Statistical analysis

SAS university edition (SAS institute, Cary, NC, USA) was used for statistical analysis. Statistical significance was accepted at $P < 0.05$. The distribution of all data was verified by the Wilk-Shapiro test. Normally distributed continuous variables were represented as means ± standard deviations. Of the non-normal variables the median and interquartile range was shown. Dichotomous variables were expressed as the number and percentage of positive patients. Paired tests were used to compare clinical parameters before and after cardiac rehabilitation: the paired Student t-test (normally distributed variables) and the related-samples Wilcoxon signed rank test (non-normally distributed data). The comparison between the H-HR and the L-HR group was made using independent samples tests: the independent Student t-test (normally distributed variables) and the non-parametric independent samples Mann-Whitney U test (non-normally distributed variables).

Results

Study population

Table 1 shows the baseline characteristics of all cardiac patients (n = 2203) who were referred to the ambulatory cardiac rehabilitation program. Mean age was 62 ± 11 and more than three in four were men. At the time of the first CPET, 107 subjects were in AF. None of the patients were stopped by the supervisor during CPET for medical reasons: all declared having performed maximal testing. No complications occurred during rehabilitation period. The dropout percentage in the AF group was 20%. After exclusion of the compliant participants who were no longer in AF at the time of the second CPET (after cardiac rehabilitation) and those who performed sub-maximally on one or both tests (RER < 1.1), further analysis was continued with 63 patients (Figure 1 – Flowchart of study participants). Characteristics of this study cohort are summarized in table 1. The median age was 73 (68-76). Valvuloplasty (32%) and congestive heart failure (19%) accounted for half of the referral reasons. Resting HR was normally distributed (Figure 2), as were peak HR and change in peak VO_2. Two groups were made, based on the median resting HR of 81 on the initial 12-lead ECG. The L-HR (≤ 81bpm) and H-HR (> 81bpm) groups counted 32 and 31 subjects respectively. The characteristics of both groups are shown in table 2. Before and after training, the fraction of patients in NYHA class I was higher in the H-HR group (Table 2), though not significantly. After three months of cardiac rehabilitation, the number of patients in a higher NYHA class had decreased in favor of a lower class (Table 3). However, this change was not statistically significant (p = 0.13). Arterial hypertension was more prevalent in the L-HR group. No other significant differences were found in age, gender, comorbidity, reason for referral and medication. During the course of the exercise program, the treating physician changed the doses of the β-blockers in eight patients: three start-ups (L-HR: n = 1; H-HR: n = 2), two dose increments (L-HR: n = 1; H-HR: n = 1), one dose reduction (L-HR) and two stops (H-HR).

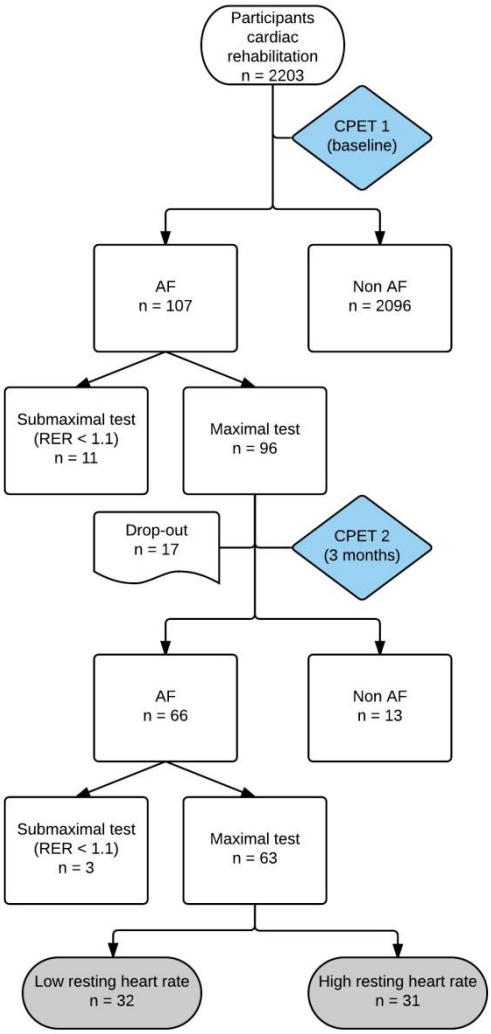

Figure 1. Flowchart of study participants

CPET = cardiopulmonary exercise testing; AF = atrial fibrillation

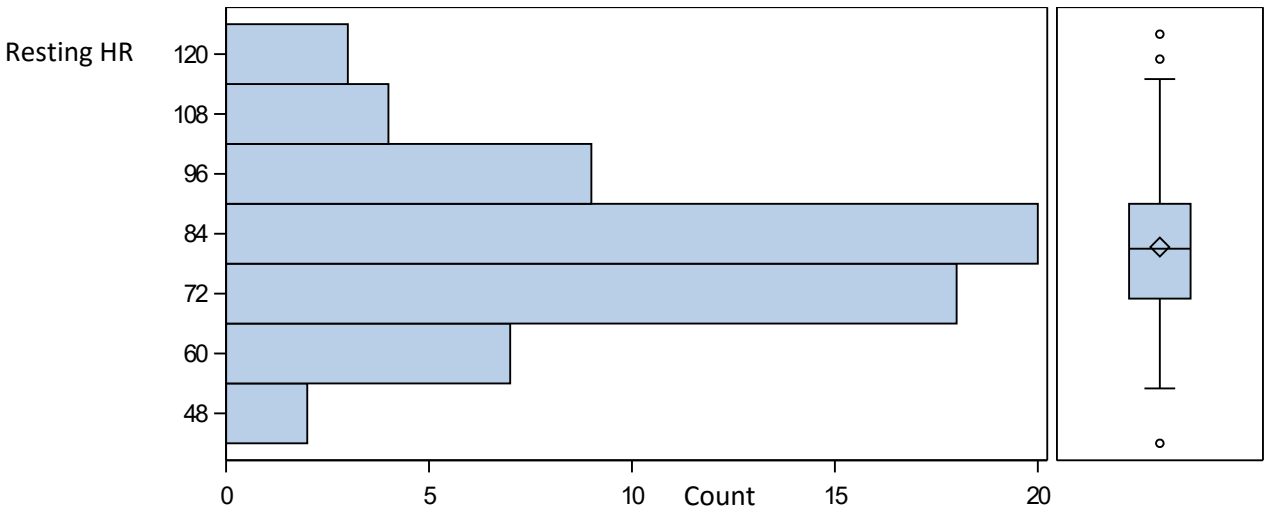

Figure 2. Distribution and probability plot for resting heart rate (HR) in permanent AF patient cohort.

Table 1. Characteristics of the total and permanent AF patient cohort.

	All (n = 2203)	Permanent AF (n = 63)
Age, mean ± SD / median (IQR)	62 ± 11	73 (68-76)
Male gender, n (%)	1695 (76.9)	48 (76.2)
Comorbidity		
Arterial hypertension, n (%)	1323 (60.1)	43 (68.3)
Diabetes, n (%)	439 (19.9)	17 (27.0)
Smoking, n (%)	1190 (54.0)	30 (47.6)
Hypercholesterolemia, n (%)	1640 (74.4)	41 (65.1)
Obesity, n (%)	658 (29.9)	21 (33.3)
LVEF (%), mean ± SD / median (IQR)	54 ± 14	50 (35-56)
Reason for referral		
Congestive heart failure, n (%)	112 (5.1)	12 (19.0)
Pacemaker, n (%)	6 (0.3)	0 (0.0)
Cardiomyopathy, n (%)	97 (4.4)	6 (9.5)
Arrhythmia, n (%)	2 (0.1)	0 (0.0)
Low Exercise capacity, n (%)	31 (1.4)	0 (0.0)
Restart cardiac rehabiliation, n (%)	8 (0.4)	0 (0.0)
Perimyocarditis, n (%)	3 (0.1)	0 (0.0)
Acute myocardial infarction, n (%)	694 (31.5)	9 (14.3)
Angor, n (%)	10 (0.5)	0 (0.0)
Heart transplant, n (%)	6 (0.3)	0 (0.0)
Aortic graft, n (%)	20 (0.9)	1 (1.6)
Coronary artery bypass grafting, n (%)	421 (19.1)	6 (9.5)
Percutaneous coronary intervention, n (%)	379 (17.2)	5 (7.9)
Implantable cardioverter defibrillator, n (%)	22 (1.0)	1 (1.6)
Valvuloplasty, n (%)	337 (15.3)	20 (31.7)
Cardiac ablation, n (%)	13 (0.6)	0 (0.0)
Other cardiovascular surgery, n (%)	23 (1.0)	1 (1.6)
Other, n (%)	19 (0.9)	2 (3.2)
Medication		
Nitrates, n (%)	45 (2.0)	1 (1.6)
Molsidomine, n (%)	83 (3.8)	6 (9.5)
Antiarrhythmics, n (%)	153 (6.9)	8 (12.7)
Digitalis, n (%)	33 (1.5)	11 (17.5)
Statines, n (%)	1750 (79.4)	44 (69.8)
Platelet aggregation inhibitors, n (%)	1774 (80.5)	29 (46.0)
Anticoagulantia, n (%)	491 (22.3)	55 (87.3)
Antihypertensives, n (%)	2066 (93.8)	61 (96.8)
Beta-blockers, n (%)	1817 (82.5)	59 (93.7)
Diuretics, n (%)	846 (38.4)	35 (55.6)
ACE inhibitors, n (%)	1204 (54.7)	31 (49.2)
Angiotensin II receptor antagonists, n (%)	268 (12.2)	7 (11.1)
Calcium channel blockers, n (%)	281 (12.8)	9 (14.3)

Table 2. Characteristics of the total permanent AF patient cohort, lower and higher resting heart rate group.

	Lower resting HR (n = 32)	**Higher resting HR (n = 31)**	***P-value***
Age, median (IQR)	72 (66-76)	75 (69-77)	0.37
Male gender, n (%)	25 (78.1)	23 (74.2)	0.71
<u>Comorbidity</u>			
Arterial hypertension, n (%)	26 (0.81)	17 (0.55)	0.02
Diabetes, n (%)	9 (28.1)	8 (25.8)	0.84
Smoking, n (%)	18 (56.3)	12 (38.7)	0.16
Dislipidaemia, n (%)	23 (71.9)	18 (58.1)	0.25
Obesity, n (%)	12 (37.5)	9 (29.0)	0.48
LVEF (%), median (IQR)	50 (28-56)	51 (35-57)	0.64
NYHA class t1 I – II – III, n (%)	13 (40.6) - 14 (43.8) - 5 (15.6)	16 (51.6) - 9 (29.0) - 6 (19.4)	0.32
<u>Reason for referral</u>			
Congestive heart failure, n (%)	6 (18.8)	6 (19.4)	
Cardiomyopathy, n (%)	4 (12.5)	2 (6.5)	
Acute myocardial infarction, n (%)	4 (12.5)	5 (16.1)	
Aortic graft, n (%)	1 (3.1)	0 (0.0)	
CABG, n (%)	4 (12.5)	2 (6.5)	
PCI, n (%)	3 (9.4)	2 (6.5)	0.38
ICD, n (%)	1 (3.1)	0 (0.0)	
Valvuloplasty, n (%)	7 (21.9)	13 (41.9)	
Other cardiovascular surgery, n (%)	1 (3.1)	0 (0.0)	
Other, n (%)	1 (3.1)	1 (3.2)	
<u>Medication</u>			
Nitrates, n (%)	1 (3.1)	0 (0.0)	0.32
Molsidomine, n (%)	5 (15.6)	1 (3.2)	0.09
Antiarrhythmics, n (%)	6 (18.8)	2 (6.5)	0.14
Digitalis, n (%)	4 (12.5)	7 (22.6)	0.29
Statines, n (%)	23 (71.9)	21 (67.7)	0.72
Platelet aggregation inhibitors, n (%)	16 (50.0)	13 (41.9)	0.52
Anticoagulantia, n (%)	28 (87.5)	27 (87.1)	0.96
Antihypertensives, n (%)	31 (96.9)	30 (96.8)	0.98
Beta-blockers, n (%)	29 (90.6)	30 (96.8)	0.32
Diuretics, n (%)	17 (53.1)	18 (58.1)	0.69
ACE inhibitors, n (%)	19 (59.4)	12 (38.7)	0.10
ARBs, n (%)	4 (12.5)	3 (9.7)	0.72
Calcium channel blockers, n (%)	5 (15.6)	4 (12.9)	0.76

LVEF: Left ventricular ejection fraction; IQR: interquartile range;
CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention;
ICD: Implantable cardioverter defibrillator; ARBs: Angiotensin II receptor blockers;

The level of statistical significance of the comparison of the L-HR and the H-HR group is shown by the p-value in the right column.

Cyclo-ergometry results before and after cardiac rehabilitation

The results of CPET at baseline and after cardiac rehabilitation were summarized in table 3. In all, a mean decrease in resting HR of 3 bpm was seen after a three month exercise program. The mean chronotropic competence (difference between peak HR and resting HR) increased with 10 bpm. An average increase in peak VO_2 of 22% was noted. The mean increase of maximum oxygen utilized per kg of body weight was 3ml/kg/minute. The mean percentage of predicted VO_2 was 68 at baseline and increased to 81 after cardiac rehabilitation. On average, patients endured CPET for one minute longer than before training.

When comparing the L-HR and the H-HR group, no significant differences were found in peak VO_2 before or after training. The second CPET showed that the training related absolute and relative increase in peak VO_2 and exercise duration were similar in both groups. Compared to their predicted peak oxygen uptake, H-HR patients performed better (Figure 3). This difference was seen both before and after the training program but was not significant.

Peak HR increased significantly in the H-HR group and became significantly higher than peak HR in the L-HR group after training. In contrast to the L-HR group, a clear decrease in resting HR was seen in the H-HR group. These last two findings resulted in an increase in chronotropic competence in the H-HR group. Blood pressure and its evolution were not different within any group at the first or the second test.

No significant correlation (table 4) was found between resting HR and peak-VO_2 before (Pearson's $r = 0.04$, $P = 0.74$) or after (Pearson's $r = -0.02$, $P = 0.91$) exercise training. There was a small and non-significant tendency towards negative correlation between resting HR and change in peak VO_2 after exercise training (Pearson's $r = -0.13$, $P = 0.31$). The same goes for the difference in resting HR and peak VO_2 before (Pearson's $r = -0.16$, $P = 0.22$) and after (Pearson's $r = -0.13$, $P = 0.33$) exercise training. This was also the case for resting HR and chronotropic competence at baseline (Pearson's $r = -0.14$, $P = 0.28$). A significant negative correlation was found between resting HR and the difference in resting HR (Pearson's $r = -0.61$, $P < 0.0001$).

Table 3. Cardiopulmonary exercise testing results before (1) and after (2) cardiac rehabilitation in permanent AF participants, lower and higher heart rate group.

	All	Lower resting HR	Higher resting HR	*P value*
Resting HR t1 (bpm)	81 ± 16	69 ± 9	94 ± 12	<0.0001
Resting HR t2 (bpm)	77 (70-85)	73 (67-79)	82 (72-77)	<0.01
Δ resting HR (bpm)	-2,7 ± 15	4,5 ± 11 (*)	-10,1 ± 15 (**)	<0.0001
Peak HR t1 (bmp)	129 ± 32	122 ± 31	135 ± 32	0.11
Peak HR t2 (bmp)	136 ± 32	127 ± 30	146 ± 32	0.02
Δ peak HR (bpm)	7,6 ± 23	4,4 ± 22 (NS)	11 ± 24 (*)	0.27
Peak HR 1 - resting HR1 (bpm)	48 ± 30	54 ± 28	41 ± 31	0.11
Peak HR t2 - resting HR t2 (bpm)	58 ± 30	53 ± 28	62 ± 32	0.25
Δ chronotropy (bpm)	10 ± 23	-0,03 ± 20 (NS)	21 ± 21 (***)	<0.01
Peak VO_2 t1 (ml/minute)	1029 (852-1313)	1070 (860-1320)	1006 (844-1294)	0.84
Peak VO_2 t2 (ml/minute)	1217 (1044-1604)	1331 (1048-1579)	1180 (1026-1691)	0.72
Δ peak-VO_2 (ml/minute)	223 ± 183	228 ± 188 (***)	219 ± 181 (***)	0.84
Peak VO_2 / weight t1 (ml/minute/kg)	13 (11-16)	13 (10-18)	14 (12-16)	0.47
Peak VO_2 / weight t2 (ml/minute/kg)	16 (13-19)	16 (13-20)	16 (14-19)	0.81
Δ peak VO_2 / weight (ml/minute/kg)	3 ± 3	3 ± 3 (***)	3 ± 2 (***)	0.70
Mean % of predicted VO_2 t1	68 ± 17	66 ± 17	69 ± 17	0.40
Mean % of predicted VO_2 t2	81 ± 22	80 ± 22	83 ± 22	0.54
Δ mean % of predicted VO_2 t2	14 ± 12	14 ± 12 (***)	14 ± 12 (***)	0.97
Δ exercise duration (minutes)	1 (1-2)	1 (1-2) (***)	1 (1-2) (***)	0.92
NYHA class, t2				
I, n (%)	40 (63.5)	19 (59.4)(NS)	21 (67.7)(NS)	
II, n(%)	17 (27.0)	9 (28.1)(NS)	8 (25.8)(NS)	0.67
III, n (%)	6 (9.5)	4 (12.5)(NS)	2 (6.5)(NS)	
Systolic BP at rest (bpm) t1	124 ± 19	123 ± 20	124 ±17	0.83
Systolic BP at rest (bpm) t2	122 ± 18	124 ± 19	121 ± 17	0.51
Δ systolic BP at rest (bpm)	0,27 ± 26	0,28 ± 21 (NS)	0,26 ± 30 (NS)	0.42
Peak systolic BP (bpm) t1	141 ± 26	142 ± 28	140 ± 25	0.76
Peak systolic BP (bpm) t2	144 ± 28	147 ± 30	142 ± 25	0.54
Δ peak systolic BP (bpm)	8 ± 30	9 ± 31 (NS)	7 ± 31 (NS)	0.75

HR = heart rate; t1 = baseline measurement; t2 = measurement after cardiac rehabilitation; bpm = beats per minute; Δ = difference between the first and second exercise test; BP = blood pressure; NYHA = New York Heart Association (classification).

The levels of statistical significance of the differences between the first and the second exercise test in each group are shown next to the values: NS (not significant), * (P-value < 0.05), ** (P-value < 0.01), *** (P-value < 0.0001). The level of statistical significance of the comparison of the L-HR and the H-HR group is shown by the p-value in the right column.

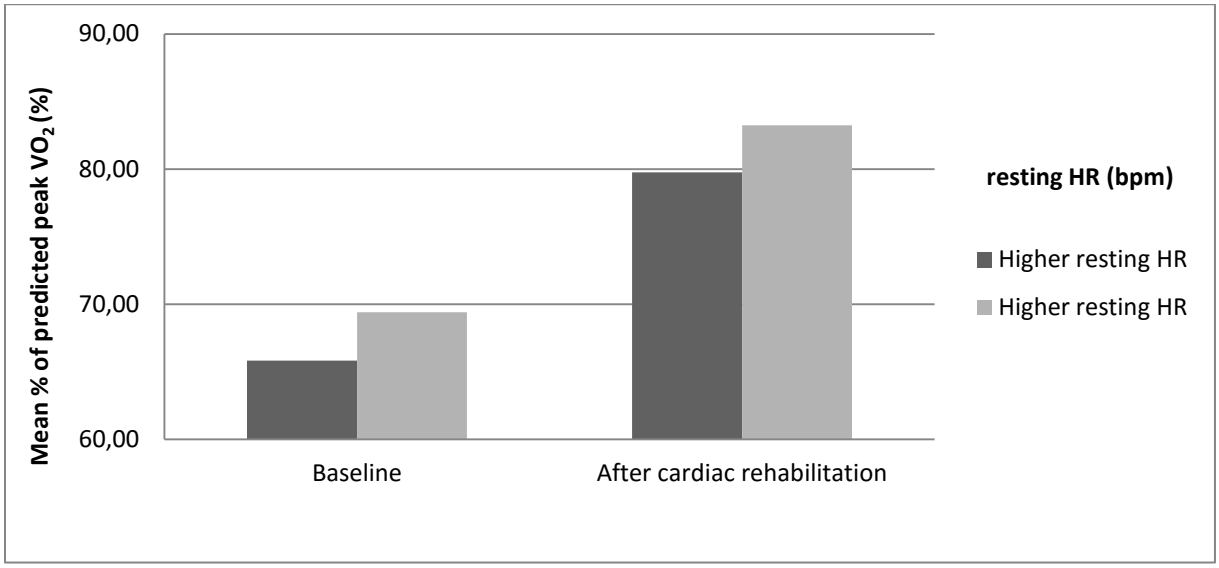

Figure 3. Relationship between resting heart rate (HR) and mean percentage of predicted peak oxygen consumption (VO_2), before and after cardiac rehabilitation.

	Resting HR	Peak VO_2 t1	Peak VO_2 t2	Δ Peak VO_2	Δ Chronotropy t1	Δ Resting HR
Resting HR	1.00000	0.04306 0.7376	-0.01503 0.9069	-0.13075 0.3071	-0.13739 0.2829	-0.61242 <.0001
Δ Resting HR	-0.61242 <.0001	-0.15530 0.2242	-0.12507 0.3287	0.01797 0.8888	0.02371 0.8537	1.00000

Table 4. Pearson correlation coefficients and their probability.
t1: before cardiac rehabilitation; t2: after cardiac rehabilitation; Δ: difference between the first and second exercise test.

Discussion

Summary of the most important results

To our knowledge, this is the first study to compare resting HR and exercise performance in relation to a cardiac rehabilitation program. The AF patients in this study made a significant progress of 21 ± 18% in peak oxygen uptake at maximal exercise testing after a three month cardiac rehabilitation program. Furthermore, the maximal duration of exercise was one minute longer. Improvement in exercise capacity was comparable in the L-HR and the H-HR group. Both study groups presented similar peak VO_2 values before and after training. Exercise performance and its evolution were not significantly correlated with resting HR, nor with change in resting HR, by training. However, our results suggest a benefit for the H-HR group. H-HR subjects in this group fulfilled a greater fraction of their predicted peak oxygen consumption, both before and after the exercise training program. The

H-HR group gained in chronotropic competence, due to an increase in peak HR and a decrease in resting HR. The higher the initial HR in the high resting HR group, the more it decreased.

Findings in context of previous research

Our findings that exercise training has functional benefits in AF patients, are in line with recent literature[38-39,43]. For example, Mertens and Kavanagh[37] found an increase in peak oxygen uptake of 15% in a group of AF patients after a one year training program. Vanhees et al.[40] found an increase in peak VO_2 of 31% in a similar training program and at the same rehabilitation center as our study. This is a greater progress in exercise performance than we found. However, it should be noted that our study had a five times higher number of participating AF patients and might therefore be more accurate.

Hegbom et al.[44], Osbak et al.[45] and Vanhees et al.[40] found a training related decrease in resting HR of 7, 9 and 12 bpm respectively. In our study results, this reduction was only objectified in the high resting HR group (-10 bpm) and in the overall AF population (-3 bpm). Literature states that regular exercise can lead to decreases in or elimination of β-blocking medication[39]. However, this was not reflected in our results. This might be due to the short duration of the exercise program and the retrospective character of the study, which was not designed to evaluate whether dose adjustments were possible. Indirectly, the good results in the H-HR group do favor the approach of reducing pharmacological doses. The same HR lowering effect can be attained using a lower dose in combination with training.

Although the training induced decrease in NYHA class in our AF population was not statistically significant, it is in line with the evidence that increased exercise capacity leads to a better quality of life[39]. Since the mean resting HR and baseline NYHA class in our AF group were already relatively low, it is possible that more progress can be made in a population with more symptoms and / or higher resting HR. Furthermore, baseline characteristics of both study groups were very similar and are therefore unlikely to explain the changes in exercise testing results.

As is the case in our study, recent literature does not show better peak-VO_2 or fewer symptoms in AF patients with a lower resting HR[32-34]. Moreover, our results match with a recent study by Kato et al.[35], who found a positive correlation (P_{trend} = 0.032) between resting HR and percentage of predicted peak oxygen consumption in AF patients. Both at baseline and after training, our high resting HR group scored a higher percentage of predicted peak VO_2. These findings are in contrast with the better exercise performances associated with lower resting HR, as seen in non-AF patients[22-24,35].

In contrast to our initial hypothesis, the higher and lower resting HR group made comparable training progression. Therefore, AF patients with a higher resting HR should also be encouraged to take part in physical training programs, even if it is harder to design proper training zones based on irregular and higher HR. Keeping in mind the often challenging pharmacological management of patients with higher resting HR, exercise training can be an important addition in terms of comfort and medical costs[5-7,45]. Although rate control remains an important part of treatment in permanent AF, our findings call for a more tolerant attitude towards higher resting HF. If our results are repeated, patients in the therapeutic rate control zone (≤ 100bpm)[35] should not be pharmacologically treated to further reduce HR. Furthermore, as stated by Jaber et al.[46] and supported by our results, strict HR control might lead to chronotropic incompetence during exercise, compromising the cardiac output.

Future research

To determine guidelines concerning physical exercise in AF patients, there are currently only few studies available and they are mostly small in sample size. It was our goal to detect any differences in AF patients between a L-HR and H-HR group. However, no assumptions can be made about what the ideal HR target range for rate control might be. Further research is needed in permanent AF patients, to investigate target HR and the best rate control management. For example, when pharmacologically targetting an initial rate control of < 100bpm, additional HR reduction could be reached by exercise training. Pharmacologically pursuing a lower HR from the start, might be preserved for only those AF patients who do not (wish to) participate in cardiac rehabilitation. When considering implementation of cardiac rehabilitation as a (reimbursed) part of permanent AF treatment, additional large randomized controlled trials and a cost-benefits analysis are needed.

Limitations of the study

A few limitations should be noted. It is a retrospective study, with a relatively small study sample. Because of the retrospective nature of the study, adjustments in β-blocker doses were not aimed nor controlled for. Another, more severe, definition of maximal exercise testing was used (RER < 1.1) than in for example the recent study of Kato et al.[35] (RER < 1.0). The fraction of drop-outs was comparable to a similar study in our center[40]. The analyzed groups were not randomized, as the group assignments depended on the initial resting HR median. Considering this median and the normal distribution of resting HR in our patient cohort, ventricular rate control at baseline was reasonably good in our study. Therefore, it is possible that different results would be obtained in a group with a higher mean resting HR and more symptoms. Moreover, only subjects who followed the rehabilitation program and agreed to perform maximal exercise testing were included in the study. Following these limitations, extrapolation of these results to the general permanent AF population should be made with caution.

Conclusion

Our study results in permanent AF patients confirm a prominent increase in exercise capacity after a three month exercise training program, without adverse events. Resting heart rate was not correlated with trainability. Patients with a higher resting HR at baseline did not make less progress. Rather, they scored a higher percentage of predicted peak oxygen uptake before and after training. These findings favor a less stringent pharmacological rate control policy, in combination with encouragements to engage in exercise therapy. Further research is needed to optimize the balance between the pharmacological and physiological heart rate lowering treatment by exercise training.

Abbreviations in text

CPET: cardiopulmonary exercise testing

HR: heart rate

H-HR: higher resting heart rate (group)

L-HR: lower resting heart rate (group)

NYHA: New York Heart Association (classification)

Disclosures

There are no potential conflicts of interest to declare.

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Attachments

Appendix 1 - Populaire samenvatting

De onderzochte populatie in deze masterproef betreft hartpatiënten die lijden aan een aanhoudende vorm van voorkamerfibrillatie ("VKF"). Dat is een frequente hartritmestoornis die kan leiden tot verminderde inspanningsmogelijkheden. In onze studie wilden we evalueren of deze patiënten baat zouden kunnen hebben bij het volgen van een fysiek trainingsschema voor hartpatiënten, een "cardiaal revalidatieprogramma". Het opstellen van adequate trainingsschema's voor deze patiënten is vaak moeilijk. Zo'n plan wordt namelijk ontwikkeld o.b.v. hartslag-trainingszones. Dat is echter een grotere uitdaging wanneer de hartslagfrequentie onregelmatig en hoger dan gemiddeld is, zoals bij dit ritmeprobleem. We waren ook geïnteresseerd in een mogelijk verschil in uitkomst tussen patiënten met een initieel hogere of lagere hartslagfrequentie in rust. Mogelijks zouden patiënten die al bij aanvang een hoge rusthartslag hebben, bij inspanning sneller aan hun maximum zitten en dus minder goed kunnen presteren. Hun hart kan immers niet meer voldoende zuurstof naar het lichaam pompen eens het niet meer kan versnellen. Bij mensen zonder ritmestoornis zien we n.a.v. zo'n oefenprogramma doorgaans o.a. een daling van de rusthartslag en een toename van de maximale inspanningscapaciteit. Er is nog niet veel onderzoek gebeurd naar deze relaties specifiek in patiënten met deze ritmestoornis. Het is niet ondenkbaar dat de patiënten bij wie de rusthartslag moeilijker 'gekalmeerd' kan worden tot een lagere frequentie, ook minder winst zouden kunnen boeken door fysieke training en dus minder "trainbaar" zijn. Zo stelde zich de vraag of conditieverbetering door training in verband staat met met de rusthartfrequentie bij patiënten in aanhoudende VKF.

Om dit alles goed te kunnen meten en oplijsten werd beroep gedaan op de kennis en kunde van de afdeling cardiale revalidatie van het UZ Leuven. Zij stonden onder meer in voor de begeleiding van de trainingssessies en voor het afnemen van de maximale fietsproeven. Zo'n inspanningstest op de fiets is nodig om een aantal parameters te bepalen om een uitspraak te kunnen doen over de (evolutie in) hartslag en inspanningsvermogen. In onze studie werden deze patiënten met aanhoudende VKF twee keer gevraagd om deze test af te leggen. De eerste keer bij aanvang van het trainingsprogramma en de tweede keer na drie maanden vordering. We verdeelden deze patiënten in twee groepen o.b.v. hun eerste resultaten: 32 mensen in de "lage" rusthartslag-groep" (≤ 81 slagen/minuut) en de 31 anderen in de "hoge" rusthartslag-groep.

Analyse van de resultaten leerde ons dat de beschreven ritmestoornispatiënten er gemiddeld meer dan 20% op vooruit gingen na drie maanden training. Opmerkelijk hierbij was dat de inspanningsmogelijkheden bij aanvang en de verbetering in conditie niet relevant verschilden tussen

de beide studiegroepen. Rusthartslag bij aanvang was dus geen voorspeller van de mate waarin iemand trainbaar bleek. In de groep met hogere rusthartslagfrequentie bij aanvang, zagen we bovendien een duidelijke toename in “hartslagreserve”, dat is het verschil tussen je hartslag in rust en je hartslag bij maximale inspanning. Daarnaast traden er ook geen complicaties op tijdens de trainingen of fietsproeven, hetgeen de idee ondersteunt dat deze patiënten op een veilige manier hun trainingsschema kunnen afwerken. De resultaten van deze studie suggereren dat cardiale revalidatie een vast (terugbetaald?) onderdeel kan worden van de behandeling van patiënten met aanhoudende VKF. Daarnaast pleiten deze gegevens ook voor een minder strenge omgang met een iets hogere rusthartslagwaarde, al wordt wellicht wel best vastgehouden aan een maximale grenswaarde voor harstlagfrequentie in rust (bv. 100 slagen/minuut). De ideale hartslagfrequentie voor deze patiënten is nog niet gekend en ook een grote kosten-baten-analyse werd nog niet uitgevoerd. Er is dus nog meer onderzoek nodig om de preciese plaats te bepalen van cardiale revalidatietraining bij aanhoudende VKF.

Appendix 2 – Guidelines for authors

European Journal of Preventive Cardiology

The European Association for Cardiovascular Prevention & Rehabilitation

Hyperlink:

https://uk.sagepub.com/en-gb/eur/journal/european-journal-preventive-cardiology#submission-guidelines

Appendix 3 - Ethical committee

Approval

Van: Simon Brumagne <simon.brumagne@faber.kuleuven.be>
Verzonden: woensdag 13 januari 2016 9:24
Aan: Kaatje Goetschalckx
CC: Christophe Mortelmans
Onderwerp: Betreft uw aanvraag Ethische begeleiding masterproeven met titel "Rusthartfrequentie bij voorkamerfibrillatie: predictief voor trainbaarheid?" (mp10324)

English version below

Geachte Heer/Mevrouw

De Opleidingspecifieke Ethische Begeleidingscommissie van de opleiding "Master in de sportgeneeskunde (Leuven)" heeft uw voorstel tot Masterproef "Rusthartfrequentie bij voorkamerfibrillatie: predictief voor trainbaarheid?" onderzocht en gunstig geadviseerd. Dit betekent dat de commissie van oordeel is dat de studie, zoals beschreven in het protocol, wetenschappelijk relevant en ethisch verantwoord is. Dit gunstig advies van de commissie houdt niet in dat zij de verantwoordelijkheid voor de geplande studie op zich neemt. U blijft hiervoor zelf verantwoordelijk. Indien u van plan bent uw masterproef te publiceren kan deze e-mail dienen als bewijs van goedkeuring.
Dear Mr/Ms

The Supervisory Committee on Medical ethics of the "Master in de sportgeneeskunde (Leuven)" programme has reviewed your master's thesis project proposal "Rusthartfrequentie bij voorkamerfibrillatie: predictief voor trainbaarheid?" and advises in its favour. This means that the committee has acknowledged that your project, as described in the protocol, is scientifically relevant and in line with prevailing ethical standards. This favourable advice does not entail the committee's responsibility for the planned project, however. You remain solely responsible. If you intend to publish your master's thesis, this e-mail may be used as proof of the committee's consent.
Met vriendelijke groeten
Opleidingsspecifieke begeleidingscommissie van de opleiding Master in de sportgeneeskunde (Leuven)

Application

Rusthartfrequentie in voorkamerfibrillatie: predictief voor trainbaarheid?

Achtergrond:

Cardiale revalidatie komt de fitheid van de patiënt ten goede. Dit kan worden geobjectiveerd m.b.v. een maximale inspanningstest: men verwacht dat de hartfrequentie benodigd voor een bepaald activiteitsniveau afneemt in de loop van de revalidatie.

Vraagstelling:

In deze masterproef zal worden onderzocht of er bij patiënten met voorkamerfibrillatie een verband is tussen de rusthartfrequentie bij aanvang van de revalidatie enerzijds en de maximale inspanningscapaciteit bij start van het programma evenals de trainbaarheid van de rusthartslag na

drie maanden. We willen nagaan of de VKF-patiënten met een hogere initiële rusthartslag al dan niet een kleinere progressiemarge hebben en of er reeds bij aanvang een verschil in prestatievermogen bestaat.

Methodologie:

Voorafgaand aan de verwerking van de bestaande gegevens zal een literatuurstudie worden uitgevoerd. Bij de patiënten op afdeling cardiale revalidatie van het UZ werd na één en drie maanden een maximale inspanningstest uitgevoerd. Deze gegevens (incl. antropometrie, cardiovasculaire risicofacoren, medicatieklasse) werden opgeslagen in een database. De patiënten met voorkamerfibrillatie (chronisch of indien tweemaal op moment van inspanningstest) zullen worden geselecteerd. Aanvullend worden gegevens toegevoegd die beschikbaar zijn uit andere consultaties in het UZ (bv. ECG in rust, ejectiefractie). Vervolgens zullen statistische correlaties worden onderzocht en beschreven. Dit gebeurt in samenwerking met de promotor en de revalidatiekinesist.