Effects of cardiac rehabilitation on functional capacity and quality of life in patients with normal and impaired left ventricular function

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Chapter 1
Exercise treatment of cardiac patients
From bed rest in all towards tailored cardiac rehabilitation programs
Chapter I

Exercise treatment of cardiac patients

PREFACE

The role of exercise in patients with cardiac disease has changed dramatically this century. From absolute bed rest after myocardial infarction and restriction of physical activity, exercise training has become a well-established modality of treatment in patients after a recent myocardial infarction and other cardiac conditions, especially as part of a multidisciplinary cardiac rehabilitation program. These changes are described in this chapter. The actual position of cardiac rehabilitation will be disclosed by a review of the literature. First the literature will be discussed from the standpoint of outcome assessment. A lot of different parameters were used, which can partly be explained by the multi-levelled goal setting in cardiac rehabilitation. Next the influence of patient characteristics on outcome of cardiac rehabilitation will be discussed and at last the influence of different characteristics of the cardiac rehabilitation program itself. The rationale of the present dissertation will be explained by the actual theme in cardiac rehabilitation, “tailor-made, individualised”, with the presented literature review in mind.

INTRODUCTION

“Rest for a diseased organ ... is a therapeutic principle validated by clinical experience. ...When the heart is diseased, the only feasible application of the principle of rest is the attempted diminution of the cardiac load”1. With these words Levine opened in 1952 his paper, that proposed the armchair treatment, an alternative approach for complete bed rest for weeks after a myocardial infarction. The recommended treatment consisted of periods of increasing length sitting in “a comfortable mobile chair” already within the first week after myocardial infarction. Primary goal of this treatment was to “..achieve more rest for the heart..” by “..diminution of the cardiac load..” and certainly not increasing “..activity of the patient”. Therefore, this treatment was not a true rehabilitation program. Nevertheless, Levine’s treatment is generally considered as the start of a new era for exercise treatment in cardiac patients and he observed already “..beneficial effects on the psychological..” and “..facilitation of the rehabilitation process”1. However, soon after the paper of Levine, Newman promoted a true cardiac rehabilitation program (“A program of rehabilitation for patients suffering from acute myocardial infarction ....involve the co-ordination of psychotherapeutic and physical and occupational therapeutic activities. It is felt that such a program makes for much better physician-patient relationship, decreases the tendency to anxiety, and prevents general physical deconditioning of the patient.”)2. Although their program became dated and looks nowadays very old-fashioned and sometimes even ridiculous, the concept and the objectives of their program were revolutionary and should be considered as a major turning point in the history of cardiac rehabilitation.
1.1 HISTORICAL PERSPECTIVE

Already in ancient history exercise was advised for prevention and treatment of various conditions. The first accurate descriptions of exercise as treatment modality can be traced back to Hippocrates. His recommendations regarding exercise were rather modern. He prescribed for example interval training and advised an individualised approach. The character of all these advises was (primary) preventive. Galenus (2nd century) used exercise treatment for rehabilitation of patients who had become weak due to severe illness³.

Beneficial effects of exercise training were emphasised again in the 18th century. Heberden was the first who described the effects of exercise training in cardiac patients. He reported in 1768 that angina pectoris was nearly cured after 6 months of sawing wood for half an hour a day. In the 19th century some form of exercise training of patients with heart disease was used in spa centres, for example Bad Nauheim⁴. However, after the description of myocardial infarction by Herrick in 1912 bedrest for a period of 2 months or longer was practised in patients after myocardial infarction for decades. This approach began to change in the late forties, when the chair therapy was promoted in order to reduce preload¹. Although the rationale for chair-therapy was a reduction of cardiac work, it was a start of development of early ambulation after myocardial infarction and of exercise training in cardiac patients². Gradually in more countries exercise training was applied in a growing number of patients. Especially after the seventies the development was fast. A great variety of exercise training programs has been applied ever since. Differences in programs can be explained for a part by local factors (e.g. infrastructure, travel-distances, health-care system, personal beliefs and insight).

Developments in the Netherlands

Also in the Netherlands a great variety of programs has been developed during the past 30 years. The nineties are characterised by two trends. The first is a call for unity in indications for cardiac rehabilitation and in objectives of cardiac rehabilitation⁵. Consensus about indications and objectives is required to clarify the position of cardiac rehabilitation to third party payers, to the government, and to the referring cardiologists and general practitioners. The second trend was the urge for so called individualised, tailored cardiac rehabilitation⁶. In individualised, tailored programs cardiac rehabilitation is modified or tailored to the individual needs and possibilities of the patient. Both developments can be complementary and should guarantee an effective and economic use of the available infrastructure⁵. The call for individual tailored programs will grow further in response to, for example, an increasing individuality and heterogeneity of patients referred. In order to develop individualised tailored cardiac rehabilitation programs, it is required to know which modifications in the program should be made for which patient. To put it in other words: which program is appropriate for which type of patient. Therefore, it is important to improve our knowledge of the effects of different programs and determinants predicting the outcome of cardiac rehabilitation in general and in different programs in particular.
§ 1.2 OVERVIEW OF LITERATURE

Structure
The overview of the literature will focus first on outcome assessment. Next issue will be the influence of patient characteristics on main effects of a cardiac rehabilitation program. At last the influence of the different constituents of cardiac rehabilitation program itself will be discussed. Cardiac rehabilitation has become a multi-disciplinary treatment and the exercise training part is just one of the program. However, it is in most programs still the mainstay. Although this overview will discuss various parts of a cardiac rehabilitation program, it will focus on the exercise training.

§ 1.2.1 Outcome
The WHO focused on restoration of normal daily functioning and “resuming a place as normal as possible in the life of community” in their first definition of cardiac rehabilitation in 1969. This definition is nowadays extended with retaining this place in community and control of risk factors for coronary heart disease.

WHO 1993
Needs and action priorities in cardiac rehabilitation and secondary prevention
in patients with coronary heart disease.

Definition of cardiac rehabilitation:
the rehabilitation of cardiac patients is the sum of activities required to influence favourably the underlying cause of the disease, as well as to ensure the patients the best possible physical, mental and social conditions so that they may, by their own efforts, preserve, or resume when lost, as normal a place in the life of the community. Rehabilitation can not be regarded as an isolated form of therapy, but must be integrated with the whole treatment, of which it forms only one facet.

The objective of cardiac rehabilitation was described in general terms in this definition, which gives the opportunity for a broad interpretation. Outcome assessment is therefore still a difficult problem in cardiac rehabilitation; a preserved or resumed normal functioning is hard to define and hence difficult to measure. Therefore, most trials focus on just an isolated factor of the problems of the patient. The various factors to be evaluated can be categorised in several terms: i.e. medical-biological (morbidity/mortality, exercise capacity), psychosocial, or parameters of secondary prevention (lifestyle, medical treatment of risk factors). Evaluating only one isolated factor may create the problem of over- or underestimation of the efficacy of cardiac rehabilitation. The choice of an outcome parameter is therefore a critical decision in assessing efficacy of cardiac rehabilitation. Discrepancies in findings of different studies on cardiac rehabilitation may relate more to problems with assessment than to the treatment itself.
The WHO-model of impairment-disability-handicap approaches (cardiac) rehabilitation theoretically and is especially used for the purpose of establishing the rehabilitation diagnosis. The goal of rehabilitation can be formulated with this diagnosis in the individual patient. This might offer a tool in evaluating efficacy of treatment. However, it is difficult to summarise this model into one (hard) endpoint, which can be easily and objectively monitored. It is therefore difficult to apply this model in trials.

§ 1.2.1.1 Medical-biological outcome

As mentioned above, one of the primary goals of cardiac rehabilitation is the return of the individual to optimal functioning, both psychological and physiological. Most parameters used evaluate a part of this functioning or an intermediate goal. Different medical-biological parameters are used and they can be categorised in two main categories, i.e. morbidity/mortality and exercise capacity. Left ventricular function might be considered also as a main outcome with this respect, as it is an important condition to obtain a situation of normal physiological functioning and because of the initial concerns for deterioration after myocardial infarction. In addition, other medical-biological parameters were reported. However, they assess working mechanisms to explain or elucidate the effect of cardiac rehabilitation or exercise training on main outcome (table 1). This overview will focus on the three main categories and the other parameters are not extensively mentioned.

<table>
<thead>
<tr>
<th>Intermediate goals or effects</th>
<th>References</th>
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<tr>
<td>Skeletal muscle metabolism</td>
<td>+ Ades 41, Hambrecht 42, Stratton 43, Sullivan 40</td>
</tr>
<tr>
<td>Peripheral vascular function / hemodynamics</td>
<td>+ Coats 19, Sullivan 40</td>
</tr>
<tr>
<td>Respiratory muscle strength / pulmonary function</td>
<td>+ Mancini 38, Coats 19, Davey 39</td>
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<tr>
<td>Myocardial perfusion</td>
<td>+ Belardinelli 30, Haskell 28, Froelicher 31</td>
</tr>
<tr>
<td>Coronary collaterals</td>
<td>+ Belardinelli 29</td>
</tr>
<tr>
<td>Myocardial O₂ demand (as reflected by RPP) at sub-maximal levels of physical activity</td>
<td>+ Ades 36,37, Varnauskas 34</td>
</tr>
<tr>
<td>Progression of atherosclerosis</td>
<td>- Niebauer 26; Gould 27; Haskell 28</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>+ Tran 15, Lavie 16, Hambrecht 17</td>
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<tr>
<td>Obesity</td>
<td>- Blair 29, Lavie 16, Lavie 24, Wilhelm 25</td>
</tr>
<tr>
<td>BP at rest</td>
<td>+ Martin 32, Marceau 33, Varnauskas 34, Wilhelm 25, Hamalainen 35</td>
</tr>
<tr>
<td>Platelet activation and hyperreactivity</td>
<td>- Rauramaa 14</td>
</tr>
<tr>
<td>Endothelial function</td>
<td>+ Charo 18, Hambrecht</td>
</tr>
<tr>
<td>Autonomic function</td>
<td>+ Coats 19, Adamopoulos 20, Malfatto 21; Kiilavouri 22</td>
</tr>
</tbody>
</table>

Table 1. Medical-biological intermediate endpoints of exercise training during cardiac rehabilitation.

Abbreviations: HR = heart rate; BP = blood pressure (systolic); RPP = Rate Pressure Product (calculated by HR x BP). + = improvement or increase, - = decrease.
Reduction of (cardiac) morbidity and mortality was the most important issue in the first three decades of cardiac rehabilitation. Although beneficial effects on mortality and morbidity were assumed, it was initially difficult to demonstrate. Most studies had a too small study-sample to demonstrate an effect on morbidity and mortality\textsuperscript{25,44-46}, also because they focused predominantly on low-risk patients\textsuperscript{47}. Another problem was the study-design. Many open, uncontrolled trials were performed, because it was hard to get a good control group in a randomised way\textsuperscript{48}. Some studies used a surrogate control group. For example a control group randomised to a limited exercise training program, which was assumed to have no effect\textsuperscript{49}. Others used patients of other (remote) hospitals for control\textsuperscript{50}, matched controls\textsuperscript{51}, or randomly allocation\textsuperscript{35,52,53}. One study used randomisation but evaluated only a small population\textsuperscript{54}.

Nevertheless a reduction of cardiac morbidity and mortality was demonstrated in a number of these studies. Hedbäck demonstrated at a five-year follow-up a significant reduction in non-fatal myocardial infarctions (17.3\% versus 33.3\%) and the rate of cardiac events (39.5\% versus 53.2\%) after rehabilitation\textsuperscript{50}. This resulted not into a reduction of cardiac mortality at five years. At ten years follow-up, effects on morbidity sustained and a significant effect on total and cardiac mortality could also be demonstrated (respectively 42.2\% vs. 57.6\% and 36.7\% vs. 48.1\%). Others demonstrated also effects on cardiac morbidity\textsuperscript{35,44,51,52} and a beneficial effect on (cardiac) mortality\textsuperscript{35,53,54}. Both O’Connor and Oldridge performed a meta-analysis of more than 20 randomised trials and observed that cardiac rehabilitation after a myocardial infarction decreased significantly both overall and cardiovascular mortality throughout at least 3 years (with approximately 20\%)\textsuperscript{55,56}. The reduction of non-fatal reinfarction did not reach statistical significance in both analyses.

The above mentioned studies were mostly done in the seventies and early eighties. Since then, therapeutic options in cardiology have increased tremendously (e.g. thrombolysis, coronary angioplasty, stenting, Angiotensin Converting Enzyme inhibitors, lipid-lowering drugs, implantable cardiac defibrillator) and also prognosis has improved considerably. To what extent the data of these older trials are still applicable remains to be questioned and warrants reestablishment. However, to study mortality (and morbidity) nowadays is cumbersome. Due to a low event rate and mortality after for example a myocardial infarction, such a study will need a very large sample size. Greenland calculated that at least 4,000 participants were required to reach statistical significance\textsuperscript{47}. Another approach is, to study patients with a higher risk, for example patients with congestive heart failure. Recently, Belardinelli demonstrated in these patients a significant reduction of mortality and hospital readmission for heart failure after cardiac rehabilitation\textsuperscript{57}.

**Exercise capacity** Movement is the main manifestation of life. Parameters of the capacity to move are therefore a natural choice in outcome assessment of rehabilitation. These parameters were even more reasonable in the days cardiac rehabilitation was developed. As mentioned earlier, many patients received bed rest as cardiovascular therapy in the early seventies. After a period of bed rest patients faced a huge loss of their exercise capacity. Restoration of their exercise capacity was a first
step in resuming a more or less normal functioning. Nowadays, bed rest period is limited to the few days of the acute phase of an acute coronary event\textsuperscript{58,59} and a severely decreased exercise capacity due to deconditioning is therefore rarely observed.

Peak exercise capacity is mostly used in assessment of exercise capacity. It is measured usually during graded limited exercise test and reported in peak oxygen uptake (peak VO\textsubscript{2}), peak workload in bicycle testing, or in treadmill testing in treadmill-time, maximal speed and/or grade. Although peak workload or treadmill speed and grade reflects daily functioning more than peak VO\textsubscript{2}, peak VO\textsubscript{2} is usually preferred. It is considered to be the most objective parameter of exercise capacity\textsuperscript{60,61}. Most studies reported therefore peak VO\textsubscript{2} as the main physiologic outcome. However, many studies did not actually measure but estimated peak VO\textsubscript{2}. Especially the older studies used estimated peak VO\textsubscript{2}, using nomograms, and sometimes reported it in METS (metabolic equivalent; 1 MET = 3.5 ml/kg/min). Froelicher compared both methods and observed a substantial discrepancy. The measured peak VO\textsubscript{2} increased with 1.3 ml/kg/min or 5\% after an exercise program for patients with stable coronary artery disease, while the estimated peak VO\textsubscript{2} increased with 4.7 ml/kg/min or 18\%.

Nowadays, the six minutes walk distance is used also\textsuperscript{62}. It might however be questioned, whether the six minutes walk distance is a parameter of either peak exercise capacity or of endurance exercise capacity, or of none of them.

Parameters of endurance exercise capacity might reflect better day-to-day activities of patients. Most of these activities must be sustained for a longer period of time and are regularly at a sub-maximal level. Patients will decrease their exercise level as soon as they get symptoms of dyspnea or exertion. If restoration of normal day-to-day activities is the primary goal, as it is in most instances of cardiac rehabilitation, sub-maximal exercise capacity appears to be a more appropriate means of assessing the effects of the treatment. However until quite recently, sub-maximal endurance exercise capacity was hardly assessed. It can be evaluated for example by an endurance test at a sub-maximal workload\textsuperscript{67}. An alternative is the assessment of the anaerobic threshold. This can be measured by different methods, i.e. maximal lactate steady state, onset of blood lactate accumulation, or using ventilatory determinants\textsuperscript{61-67}. The maximal lactate steady state is determined in a number of sub-maximal endurance exercise tests. This method needs different tests at different days, is time-consuming, and is very demanding for the patient. Therefore, the use of the maximal lactate steady state is hardly feasible both in clinical practice and in trials. Also, the determination of the onset of lactate accumulation is a rather invasive test and is nowadays hardly used. The ventilatory anaerobic threshold has been described already three decades ago and different methods are proposed. Assessment of the ventilatory anaerobic threshold has become relative easy with the availability of rapid handy gasanalysers and fast microprocessors. Another advantage is that it can be determined during the same graded symptom-limited exercise test, which is also used for measurement of peak exercise capacity (including peak VO\textsubscript{2}).

Improvement of sub-maximal exercise capacity can also be evaluated by rather simple means, for example a decrease of heart rate and systolic blood pressure (combined the Rate Pressure Product) at a comparable workload. These parameters
used to be popular in earlier years, but are nowadays hardly used. At the moment a comparable parameter, the Pulse (or Physical) Working Capacity (PWC), i.e. the work capacity at a given heart rate (e.g. 110 or 130/min, respectively PWC 110 and PWC 130), is sometimes used in chronic heart failure studies\(^{68,69}\). The relative ease to assess and to compare is an important advantage of the PWC and therefore deserves more attention in future.

Endurance exercise capacity was measured only in very few studies. Ades determined the sub-maximal exhaustive endurance capacity on a treadmill, exercising at 80% of the baseline peak VO\(_2\). He demonstrated that the endurance time increased by more than 40% during 12 month exercise training in older coronary patients, while peak VO\(_2\) increased by 19%\(^{37}\). Studies assessing blood lactate concentration during exercise testing observed a decrease of the concentration lactate or a delayed onset of the increase of the blood lactate concentration after exercise training\(^{40,70,71}\). The ventilatory anaerobic threshold is increasingly being used in recent studies, especially in studies evaluating exercise programs in congestive heart failure\(^{19,42,57,72-74}\). Effects on peak and endurance exercise capacity differed in these studies. Some observed no differences\(^{19}\), while others demonstrated a higher increase of the ventilatory anaerobic threshold\(^{72-74}\) and others demonstrated a higher increase of peak VO\(_2\)\(^{42}\).

Muscle strength is another important condition for movement and the functional capacity, but was hardly evaluated. Only the last decade, strength has become a more important parameter in outcome assessment, as strength training was gradually introduced in cardiac rehabilitation programs\(^{75}\). Strength was measured by either the maximum voluntary contraction of various muscle groups or by the number of repetitions of voluntary contractions at a fixed percentage of maximal voluntary contraction\(^{76-80}\). They demonstrated that strength training could safely improve strength in most cardiac patients. In addition some studies observed, that strength training improved also peak VO\(_2\)\(^{80,81}\).

Left ventricular function. Fear for deterioration of cardiac pump function and dilation of the left ventricle used to be the main argument to prescribe bed rest after a myocardial infarction\(^1\). This fear was suggested in only one study with patients after an anterior wall myocardial infarction\(^91\). Controversies about this study were mentioned right away and remained long\(^92\), because the observed differences were small, the study was a non-randomised trial with matched controls with at entry differences in baseline characteristics, and effects were probably influenced by persistent (silent) myocardial ischaemia. Recently, this issue was thoroughly evaluated and refuted in the EAMI trial\(^93\). This trial evaluated resting left ventricular function by echocardiography and observed no deterioration of left ventricular function after an early (4 weeks) exercise training in patients following an anterior wall myocardial infarction. A tendency towards improvement was even observed in the training-group. Dubach observed also no deleterious effect of exercise training on left ventricular function and volume evaluated with magnetic resonance imaging. They included also patients after a myocardial infarction (approximately 5 weeks after either anterior or inferior infarction) with a reduced left ventricular function (ejection fraction<0.40)\(^94\).
Some studies evaluated left ventricular function to explain the increased exercise capacity after exercise training, but were unable to observe a (cor)relation. Improvements of exercise capacity were mainly attributed to adaptive changes in peripheral circulation during the usually applied short-term exercise training programs. Later studies of Sullivan with patients with chronic heart failure confirmed this observation. Also in these patients improvement of metabolism, mitochondrial density, and capillary density in skeletal muscles were demonstrated. Improvement of cardiac function itself could only be demonstrated after a training program of at least one year. Patterson observed a higher stroke-volume during exercise after a long-term program (one year), partly explained by improved peripheral circulation. Later studies reported improved myocardial perfusion and cardiac function, assessed by radionuclide testing and echocardiography.

§ 1.2.1.2 Psycho-social outcome or health related Quality of Life

In many studies on the effect of cardiac rehabilitation the primary attention was focused on medical-biological issues. Gradually, more attention was paid to psychosocial functioning and the importance of assessment of health related Quality of Life was recognised. The substantial impact of psychological factors on the pathogenesis and prognosis of cardiovascular disease was acknowledged also recently.

The beneficial psychological effects of cardiac rehabilitation, either exercise training alone or as a component of multi-factorial rehabilitation, are nowadays established. This scientific evidence is consistent with the widespread belief among cardiac rehabilitation professionals. However, these effects were long disputed first despite a number of positive and sometimes enthusiastic reports. The results of different trials were initially inconsistent and many studies lacked a randomised design.

An important problem with this respect is the choice of the psychosocial domain to evaluate and the choice of a method to assess a particular domain. As emphasised by DeNollet a number of studies lacked sensitivity of outcome measures on psychosocial effects of cardiac rehabilitation. Only measures that match the theoretically prescribed effect of cardiac rehabilitation are likely to uncover the benefits of cardiac rehabilitation in terms if Quality of Life. Therefore, assessing quality of life depends first upon an understanding of the (theoretical) effect of an intervention on the different domains. At the moment five specific psychosocial domains are recognised to be important in cardiovascular disease, i.e. depression, anxiety, personality factors and character traits, social isolation, and chronic life stress. Self-efficacy is an important sub-goal of cardiac rehabilitation and should be considered as another domain in cardiac rehabilitation. After defining the domain to evaluate, the instrument has to be chosen. Many questionnaires are available and were used. These questionnaires can be divided into two broad classes (generic and specific, respectively designed to be applicable to many illness groups, and designed to a particular condition of function).
This division conceals a conflict between a simplified and clear analysis and a broad perspective that allows comparison with other conditions\textsuperscript{100}. The choice of questionnaires is still not uniform, although some are gradually becoming ‘standard’. It should be noted however that using measures of psychopathology, such as the STAI (State Trait Anxiety Inventory) and the Beck depression score can lead to underestimates of actual changes in health related Quality of Life as a function of cardiac rehabilitation\textsuperscript{99}.

*Depression* was usually assessed by the Minnesota Multiphasic Personality Inventory (MMPI) in the first reports on cardiac rehabilitation, while recently the Beck depression became more customary\textsuperscript{105}. Also the Heart Patient Psychological Questionnaire (HPPQ) assesses depressive symptoms and in a Dutch version it is

<table>
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<th>HR QoL domain</th>
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<th>Reference (questionnaires)</th>
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<tbody>
<tr>
<td>Depression</td>
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<td>DeNollet\textsuperscript{10} (Global Mood Scale)</td>
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<td>Dracup\textsuperscript{106} (MAAS)</td>
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<td></td>
<td>±</td>
<td>Kugler\textsuperscript{105} (meta-analysis)</td>
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<td></td>
<td></td>
<td>Stern\textsuperscript{108} (MMPI)</td>
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<td></td>
<td></td>
<td>Milan\textsuperscript{i16} (MOS-SF-36)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>+</td>
<td>Dracup\textsuperscript{106} (MAAS)</td>
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<td>Kugler\textsuperscript{105} (meta-analysis)</td>
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<td>Taylor\textsuperscript{112} (STAI)</td>
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<td></td>
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<td>Milan\textsuperscript{i16} (Kelner symptom questionnaire)</td>
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<td>Oldridge\textsuperscript{110} (Beck Depression Inventory)</td>
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<td>Mayou\textsuperscript{109} (interview)</td>
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<td>Vidmar\textsuperscript{104}</td>
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\textbf{Table 2.} Effects of cardiac rehabilitation program on Health related Quality of Life

Abbreviations: Hamilton = Hamilton Depression Scale; HCS = Health Complaints Scale; HPPQ = Heart Patient Psychological Questionnaire; MAAS = Multiple Affect Adjective Scale; MAS = Manifest Anxiety Scale; MMPI = Minnesota Multiphasic Personality Inventory; MQ = Medical questionnaire; STAI = State-Trait-Anxiety Inventory. + = improvement (i.e. decrease of anxiety and depression and increased well-being etc); - = deterioration; ± = no significant effect

commonly used in the Netherlands. Especially recent studies tend to be more positive about the effects of cardiac rehabilitation on depression\textsuperscript{10,106,107}, while the older trials reported more contradictory results. Some observed little or no effect\textsuperscript{108-110}, others demonstrated significant improvement of depressive symptoms\textsuperscript{111,112}. The better results of modern studies might be caused by the fact that many programs currently used are multidisciplinary and not only exercise training is practised but also education, counselling, and stress management is part of the program.

Anxiety is a prominent symptom after an acute manifestation of cardiovascular disease. It has a direct relation with the eliciting moment and is sensitive for change by treatment. It might therefore be a good parameter of the effect of cardiac rehabilitation on psychological wellbeing. Most trials used questionnaires like the STAI and the Manifest Anxiety Scale, while in the Dutch situation the HPPQ is often used\textsuperscript{105}. Most of these trials support the conclusion that cardiac rehabilitation improves patients with respect to anxiety\textsuperscript{108,112-115}.

Beneficial effects on depression, anxiety, and well-being are at the moment broadly accepted as a result of cardiac rehabilitation\textsuperscript{105}. In addition, studies and reviews are uniform in their advice that exercise programs alone are inappropriate to improve psychological well-being, but that additional treatment, like information, counselling, relaxation therapy\textsuperscript{116}, and stress management, should be integrated with exercise training in a well designed cardiac rehabilitation program\textsuperscript{98,105}.

Personality factors and character traits, and chronic life stress have an important impact on (emotional) recovery from an acute cardiac event and also on the pathogenesis of cardiovascular disease\textsuperscript{95}. These domains are unlikely to be influenced or changed by a cardiac rehabilitation program. They influence undoubtedly the outcome of it and are important parameters to assess, if the working mechanism of rehabilitation should be revealed. However, these domains are not an important parameter in outcome assessment of cardiac rehabilitation programs.

Social support might be important in both aspects\textsuperscript{117}. It might be important to explain the effects of rehabilitation. In addition, it might be also influenced by a cardiac rehabilitation program and therefore be an outcome parameter. However, surprisingly few studies focused on the relation between social support and cardiac rehabilitation.

Self-efficacy might be an important outcome, but was until now rarely used. Patients’ perception of their capabilities to perform a specific task has been shown to be a good predictor of return to work, of functional capacity, and of exercise compliance\textsuperscript{104}. Therefore, self-efficacy is an important intermediate goal of cardiac rehabilitation, in order to restore functioning. The trials that focused on the effect of cardiac rehabilitation on self-efficacy are consistent in their findings, and demonstrate a beneficial effect\textsuperscript{101-104}.

§ 1.2.1.2.1 Return to Work.

In addition return to work might be an outcome parameter, as it is an important aspect of some patients’ functioning in community. Initially it was even a main goal of cardiac rehabilitation. However, the influence of cardiac rehabilitation was small on this outcome in large groups, because other variables (not to be influenced by cardiac rehabilitation) exerted more influence (employer attitude, prior employment status,
economic incentives, social and political issues)\(^{11}\). Although return to work remains on individual basis still an important goal in cardiac rehabilitation, it is hardly evaluated systematically.

§ 1.2.1.3 *Secondary prevention for coronary artery disease*

Cardiac rehabilitation offers a unique opportunity for risk factor modification, in particular risk factors related to life style (i.e. smoking, diet, compliance to medication, and physical activities). During cardiac rehabilitation patients can be educated, extensively supported, and encouraged to change their lifestyle and to keep these changes. The importance of risk factor modification is undoubted and should be an integral part of cardiac rehabilitation\(^8\). Whether change in lifestyle by cardiac rehabilitation can reduce coronary risk factors was initially somewhat controversial\(^{47,118,119}\), but became nowadays accepted, as efficacy was demonstrated after myocardial infarction\(^{50,53}\), after coronary bypass surgery\(^{28}\), and in patients with angiographically documented coronary artery lesions\(^{120}\). Effects were demonstrated and to a lesser extent with respect to smoking, but especially on blood lipid levels, body weight\(^{11}\).

Most favourable impact on *lipid profile* (decrease total and LDL-cholesterol and triglycerides, increase of HDL-cholesterol) was reported by studies with a multifactorial cardiac rehabilitation program (including dietary education and counselling)\(^{11,17,28,52,120-122}\). An intervention by mere exercise training improved lipid profile in a few studies\(^{25,53}\), while other trials reported no significant effect\(^{11,123}\). Physical activity is therefore considered an essential element in the non-pharmacologic therapy for improvement of serum lipids. However, the effects are inconsistent and limited. Therefore, exercise training should not be the sole intervention, but implemented in optimal lipid management, including dietary and pharmologic management\(^{11}\).

The spontaneous *smoking* cessation (or interruption) rates are usually high following a coronary event. Only a few patients continue smoking. Cessation in these patients is difficult and is usually not influenced by only exercise training\(^ {11,44,53}\). Only with multifactorial rehabilitation using specific smoking cessation strategies a further reduction of cigarette smoking can be expected\(^ {122,123}\). Patients will need individual counselling and support by physician and the rehabilitation team. Group therapy, repetition, written information, and (temporal) nicotine replacement might be of additional help during cardiac rehabilitation\(^{50,124-126}\). Evaluation of smoking behaviour was applied mostly by self-report, in only a few studies smoking cessation was verified biochemically\(^{122}\).

*Physical inactivity* has been noted as risk factor for coronary artery disease for a long time. In 1953, Morris published his classic and well-known study, in which he reported a greater incidence of coronary artery disease in sedentary bus drivers compared with the more active conductors of double-deckers\(^ {127}\). In addition, the incidence of coronary artery disease proved to be inversely correlated with vigorous leisure time activity in this population\(^{128}\). Paffenbarger demonstrated comparable results in longshoremen\(^ {129}\). Results of these classic studies were confirmed by large prospective trials, like the Harvard Alumni Study\(^{105,130,131}\) and the Nurses’ Health
Study\textsuperscript{132}. These studies demonstrated also, that the impact of other coronary risk factors increased in physically inactive persons. Another important observation was that increase of habitual physical activity levels was an important intervention in primary prevention of coronary artery disease, as it decreased (cardiac) mortality\textsuperscript{133}. Although it has been suggested that only vigorous activity (>6 METs) was associated with a reduction of mortality\textsuperscript{134}, others have demonstrated that this reduction can already be obtained with regular moderate intensity\textsuperscript{105,135-137}. Recently, Hakim demonstrated that already a daily walk of more than 2.5 kilometres reduced the risk for coronary artery disease by 50\%\textsuperscript{138}.

In addition, physical inactivity is considered also to increase the risk for cardiovascular mortality in patients with already (documented) coronary artery disease\textsuperscript{56}. Enhancement of physical activities could be obtained by cardiac rehabilitation up to 1 year after completion the cardiac rehabilitation program\textsuperscript{17,120,139}. During a longer follow-up, no effect could be observed\textsuperscript{11,140}. The problem of compliance for a longer period is further stressed by reports of negative trials on this issue\textsuperscript{35,123,141}. Motivation of patients is a key issue in changing life-style into a more active one by adoption of regular exercise in their daily life\textsuperscript{142}. Therefore, improvement of motivation is a major challenge for the staff of cardiac rehabilitation programs and strategies should be aimed at this issue\textsuperscript{142}. Such a (maintenance) strategy might be obtained by regular telephone contacts and self-monitoring diaries\textsuperscript{143}. Another cause of the low compliance is lack of equipment and facilities. In the Netherlands “Hart in Beweging”(HIB) offers an important part of these facilities. The effect of these services is at the moment a subject of study\textsuperscript{144,145}. Important problem of these services is that the use of it is limited to a selected population and it is not financially supported by health insurance, in contrast to for example Germany\textsuperscript{144}.

\section*{§ 1.2.2 Patient characteristics}

Identification of patients who might benefit most from a particular cardiac rehabilitation program or be at risk for harm, has important clinical implications\textsuperscript{146}. However, predicting outcome of cardiac rehabilitation was evaluated in only a few trials\textsuperscript{147-150}. For example, Van Dixhoorn was able to predict both success and failure with a combination of clinical information, i.e. initial level of exercise tolerance and psychosocial variables. The single most important predictor of success of cardiac rehabilitation was work status before a myocardial infarction, but it did not predict failure. In contrast, psychological variables predicted failure, but not success\textsuperscript{147}.

Most other studies focused on outcome and described only one or a few factors possibly influencing outcome. These factors will be handled individually in the paragraphs below.

\subsection*{§ 1.2.2.1 Age}

Mean age of the population referred for cardiac rehabilitation increases gradually\textsuperscript{11,16,151}. Epidemiological factors and advances of medical treatment can explain
this trend. Cardiac patients are becoming older\textsuperscript{152} and as a consequence the referred population. Also, the referring pattern changes. Older patients are or will be more referred\textsuperscript{11,16}, because expectations for a life without impairment or disabilities at old age have increased.

The influence of age on the effect of exercise training was mainly studied in a retrospective way\textsuperscript{16,37,153-155}. Peak exercise capacity (e.g. peak VO\textsubscript{2}) was substantially lower in older patients, as to be expected. However the (relative) improvement was similar with the improvement of younger patients\textsuperscript{11}. Remarkable was the low number of older patients reaching a Respiratory Equivalent Ratio (VCO\textsubscript{2}/VO\textsubscript{2}) of more than 1.00 at peak exercise. This suggests that older patients are more limited in their maximal exercise effort by non-cardio-pulmonary factors, e.g. muscular weakness or stiffness, orthopaedic complaints. Endurance exercise time was also measured by Ades and improved highly with more than 40\%. Especially patients older than 70 years demonstrated the greatest improvement at this parameter\textsuperscript{37,153}.

\section*{§ 1.2.2.2 Gender}
The low number of women attending cardiac rehabilitation can be explained only for a part by the lower incidence of ischemic heart disease\textsuperscript{154}. Especially older women are less likely to be referred for cardiac rehabilitation, because it is hardly considered by their physicians and therefore not recommended. Domestic commitments can discourage women to attend cardiac rehabilitation\textsuperscript{156}. Next, women are usually older when the first symptoms of coronary artery disease presents and because of this older age they are less likely to be referred for cardiac rehabilitation\textsuperscript{157}. However, women may expect the same benefits of rehabilitation compared with men. Improvements on exercise capacity, health related quality of life, and risk factor modification are comparable\textsuperscript{107,154,157,158}.

\section*{§ 1.2.2.3 Initial level of fitness}
Patients with a high as well as with a low initial exercise capacity can improve their exercise capacity during cardiac rehabilitation\textsuperscript{159,160}. The magnitude of the improvement seems not be determined by the baseline exercise capacity\textsuperscript{147,149}. Others demonstrated that especially patients with a low initial level of fitness would benefit\textsuperscript{160}, while others demonstrated the opposite\textsuperscript{148,150}.

\section*{§ 1.2.2.4 Cardiac diagnosis}
Efficacy of an exercise training program might be influenced by nature and extent of the cardiac disease, for instance left ventricular function or myocardial ischaemia. Initially cardiac rehabilitation was applied only in patients with preserved left ventricular function after a myocardial infarction. Patients with large transmural myocardial infarction and signs of congestive heart failure were often excluded\textsuperscript{161}. Over the past 25 years other patients were referred also for cardiac rehabilitation and beneficial effects were demonstrated after coronary surgery\textsuperscript{162-164}. Beneficial effects are recognised in more recent years in patients with congestive heart failure\textsuperscript{19,40,57,71,73,30,165-168} and have become an accepted treatment modality in these patients\textsuperscript{166,169}. Cardiac rehabilitation is also indicated after heart transplantation\textsuperscript{170-173}. 
A lot of attention was paid during the last decade to the influence of the left ventricular function on outcome of exercise training program, and reverse. Exercise training proved to be effective in both patients with a decreased or with a preserved left ventricular function\textsuperscript{174-176}. Effects tend to be slightly smaller in patients with a decreased left ventricular function, although this difference was mostly not significant\textsuperscript{70,93,177}. This smaller increase of peak VO\textsubscript{2} in patients with a decreased left ventricular ejection fraction (< 0.40) might be due to myocardial ischaemia\textsuperscript{177}. Wilson recently demonstrated that training effects on exercise tolerance is less pronounced in patients with chronic heart failure with an abnormal cardiac output response to exercise\textsuperscript{178}. These observations are however in contrast with a recent study of the European Heart Failure Training Group. They observed no correlation between training effect and indices of central hemodynamic function. Moreover, training effects were more pronounced if bicycle training was combined with callisthenics and the program lasted longer than 6 weeks\textsuperscript{174}. Nevertheless, questions remain which training protocol will be most suitable for patients with chronic heart failure. Therefore, a large controlled prospective trial regarding this issue is in development in Europe\textsuperscript{174,176}.

Patients with myocardial ischaemia during exercise improve their exercise capacity. Beneficial effects of exercise training on symptoms of angina pectoris were observed long before by Heberden in 1768. Todd focused in his study on patients with angina pectoris (limiting exercise capacity) and used a program of daily exercise at home during 1 year. Exercise tolerance increased with 51%. This increase was significantly greater than in patients randomised to treatment with atenolol but no training program\textsuperscript{139}. Nevertheless, patients with documented myocardial ischaemia might expect a smaller increase of their exercise capacity during cardiac rehabilitation than patients without ischaemia\textsuperscript{36,141,177}.

\textbf{§ 1.2.3 Program characteristics}

Cardiac rehabilitation programs differed and still differ greatly in their composition. All programs offer an exercise training, which is usually even the mainstay of the program. Therefore, frequency, duration of the sessions, and the length of the program is mainly determined by the prescribed exercise training. Nowadays, most programs are multi-factorial and are offered by a multi-disciplinary team, including social worker, dietician, physiotherapist, physician (cardiologist), nurse (practitioner), or psychologist. Although these programs are not uniform and the individual effect of each component was never evaluated, the value of a multi-factorial approach above exercise training alone is undoubted\textsuperscript{11}. Recently new treatment techniques were developed and the efficacy of them was demonstrated in cardiac rehabilitation by controlled trials, i.e. relaxation therapy\textsuperscript{179}, strength training\textsuperscript{76,78-81,180,181}, and respiratory muscle training\textsuperscript{38}.

Exercise training varied greatly both in clinical practice and trials. Differences were observed in characteristics of an exercise training program, i.e. intensity, frequency, duration, length, mode of movement and of training (interval or endurance or a combination). Only intensity and mode of training were studied in a controlled
clinical trial. These trials will be discussed in the following section. Next, other program characteristics will be evaluated in this overview by comparison of the various trials and their programs.

§ 1.2.3.1 Controlled trials comparing different programs.

The influence of intensity of exercise training on the outcome of cardiac rehabilitation was evaluated by a number of trials, also very recent studies. Older studies demonstrated no significant influence of intensity of exercise training on the improvement of exercise capacity184-186. However, in one of them the differences in intensity between both programs was very small, i.e. intensity during low-intensity program 70% of maximal heart rate and during high-intensity program 75-85%184,185. Another old, but famous study (Ontario Exercise Heart Collaborative Study) evaluated primarily, whether cardiac rehabilitation decreased cardiac morbidity184. For that purpose, patients were randomised to ‘standard’ exercise training or to a control group. This control group was offered a program with a low-intensity, expecting no effect of this intervention. This study failed to demonstrate a significant effect on the primary endpoint, cardiac morbidity (reinfarction rate). However, a sub-study of this project showed a significant superior effect of high-intensity training on exercise capacity185. Two recent studies demonstrated also a favourable effect of high intensity exercise training on exercise tolerance. The Training Level Comparison Study was especially developed to study the influence of intensity of exercise training and took efficacy of cardiac rehabilitation (versus control) as well established187. Peak VO2 increased significant only with the high intensity program, but not with the low intensity program (intensity respectively: 85% and 50% of peak VO2)188. Adachi compared both low and high intensity with a control group. The intensity of exercise training was based on the measured anaerobic threshold. The patients participating in the low intensity program performed endurance exercise training below the anaerobic threshold (at a heart rate of 80% of the anaerobic threshold), while those in the high intensity program were exercised slightly above the anaerobic threshold189. This study demonstrated also a better improvement of peak VO2 during high intensity training.

The other characteristic studied in a controlled way was interval versus endurance demonstrating superiority of interval training182,183. The impact of dimensions like frequency, mode of movement, of length of a program was until now never evaluated in a controlled way.

§ 1.2.3.2 Overview of various programs in trials.

The variety of exercise training was remarkably great on frequency and intensity, but especially on length. The shortest program took only 3.5 weeks182, while the longest program lasted 7 years190. The maximal effect in this last trial was reached after 14 months with a very high increase of the measured peak VO2 of +44%. The effect remained unchanged during the next 6 years. Summarising all these studies, there is a tendency that the longer the programs the better the effect on exercise tolerance. Recently, this was also claimed for patients with chronic heart failure, with a possible optimum between 12 and 24 weeks174. The effect of length appears to be higher than the effect of frequency or intensity of an exercise training program. This is in line with the
observations in healthy adults\textsuperscript{191,192} and underlines the importance that cardiac rehabilitation programs, lasting 6 to 12 weeks, should include strategies for their participants to adopt and maintain a physical active life-style afterwards.

*Frequency* of exercise training varied also widely, from 1 session a week\textsuperscript{49} to 5 sessions a week\textsuperscript{19,193}. Both last studies demonstrated a high improvement of peak VO\textsubscript{2}. The optimum of frequency remains a matter of debate and might be also dependent of the initial level of fitness of and the goals in the individual patients. Nevertheless, a frequency of at least 2 to 3 sessions a week will suit for most patients\textsuperscript{11}.

It is difficult to compare in the various studies the *intensity* of exercise training, due to the different methods used to calculate intensity using also different parameters\textsuperscript{160}. Mostly heart rate is used and intensity is frequently expressed as percentage of the maximal heart rate. Heart rate reserve is also used, usually according the Karvonen method\textsuperscript{194}. Other methods for calculating intensity are percentage of peak workload or peak VO\textsubscript{2} and more recently the anaerobic threshold\textsuperscript{189}. In addition, the intensity should be related to the method of exercise training, either interval or endurance training. The prescribed intensity is aimed to achieve a workload at the anaerobic threshold in endurance training. In interval training a higher intensity should be prescribed, for example even 100\% during the exercise interval\textsuperscript{161}.

In general, exercise training with higher intensities seems to elicit greater gains in increase of for example peak VO\textsubscript{2}. However, the optimal intensity remains unclear and a higher risk for injuries and cardiovascular complication should also be considered\textsuperscript{195}. This optimum might be also dependent of initial level of fitness, the cardiac diagnosis, and the goals of rehabilitation in the individual patient. For example, low intensity exercise training might be sufficient to elicit an adequate training effect for patients with severe congestive heart failure\textsuperscript{73}.

\section*{§ 1.2.4 Interaction.}

The section above demonstrated, that literature offers barely definite conclusions about the impact of different patient- and program characteristics on the outcome of cardiac rehabilitation. This holds a fortiori for the interaction of both on outcome. However, especially this last issue is for the clinical practice of utmost importance. Prescription of programs is nowadays based on generalisation of the literature and clinical beliefs, observations, and feeling. For example, patients with a multiplicity of problems (e.g. chronic heart failure, with physical deconditioning, anxiety, and social problems) will be usually referred to specialised centre offering a multi-factorial intervention by a multidisciplinary team. Evaluation of such choices can not be done with controlled trials using randomisation for ethical reasons. In addition, these trials should focus on individual responses, which are commonly lost in the mean. Evaluation on an individual basis, like DeNollet proposed, might be a solution for this last problem\textsuperscript{10}. Another approach might be a qualitative methodology of research.
§ 1.3  RATIONALE OF THE PRESENT DISSERTATION

§ 1.3.1  Background.

Individualised (tailored) cardiac rehabilitation became the main theme in cardiac rehabilitation in the late eighties and early nineties, and the concept of tailor-made cardiac rehabilitation was widely spread. However in order to apply it on an evidence based way, it is crucial that the effects of different (components of) programs are known. The paragraphs above demonstrated that the influence of many components of a cardiac rehabilitation program was not studied in an appropriate, controlled way. For example the necessary frequency of exercise training was never studied. This is of particular interest, because frequency of the program is a major determinant of a program and of its costs. Another issue hardly evaluated was the mode of movement applied during exercise training. The paragraphs above demonstrated also, that outcome assessment remained a matter of debate. This concerned not only the evaluation of the main goal of cardiac rehabilitation (i.e. normal functioning) but also of the intermediate goals (e.g. exercise capacity, health related quality of life).

The local situation determined partly our studies concerning these issues. In the rehabilitation centre Beatrixoord (Haren, Groningen), a rather unique cardiac rehabilitation program was applied in the late eighties. It was a program with a very high frequency of exercise training (5 full days a week during 6 weeks), rarely used internationally. This program was developed in the early seventies and targeted mainly return to work, the primary and only goal of rehabilitation at that moment. A full-time program was therefore a logical choice. Another reason was the local infrastructure in the region at that moment (with long travel distances) necessitating the development of in-patient rehabilitation. Although the grounds for this full-time program disappeared mostly, it still existed in the early nineties, because the clinical belief was that this high frequency treatment was superior to low frequency. This superiority was however never demonstrated in controlled trials and the greater use of treatment facilities and finances was not supported by scientific data. Therefore, the high frequency program had to be justified. On the other hand, the local infrastructure of this program created also an ideal opportunity to evaluate the influence of frequency of exercise training during cardiac rehabilitation on outcome.

§ 1.3.2  Theme of this dissertation.

Program evaluation is the central theme of this thesis, focussing especially on the comparison of a high frequency with a low frequency exercise training program of patients with coronary artery disease during a phase II out-patient multi-disciplinary cardiac rehabilitation lasting 6 weeks. Effects were evaluated on exercise tolerance, psychosocial functioning, and on modification of life style related to risk factors for coronary artery disease. Next, we evaluated whether these short-term effects were maintained at follow-up. Follow-up contained a maintenance stage of 6 weeks with 1
exercise session a week followed by an additional measurement and next controls at 3 and 12 months. In total 130 patients were included into this trial. This study was financially supported by a grant of the Netherlands Heart Foundation.

In addition, the impact of mode of movement applied during exercise training was evaluated in a sub-study (with a pilot-character), which included 38 patients. This study compared a program dominated by bicycle training with a program with a combination of bicycle and walking or jogging training on the increase of peak VO$_2$ during cardiac rehabilitation.

Actually, programs can be evaluated only when valid and widely accepted parameters for outcome assessment are available. This outcome assessment is sub-theme throughout this thesis. Especially parameters of exercise tolerance were evaluated, in particular peak VO$_2$ and the ventilatory anaerobic threshold. In addition, since effects of cardiac rehabilitation are multi-levelled like the goal-setting of cardiac rehabilitation itself, other dimensions of outcome assessment will be discussed in our articles written on this issue.

**AIMS:**

To evaluate whether high frequency exercise training during cardiac rehabilitation is superior to low frequency exercise training on exercise capacity and health-related quality of life, and changes in life-style related to coronary risk-factors, both on the short- and long-term.

To evaluate the influence of mode of movement (i.e. bicycling versus a combination of walking/jogging with bicycling) applied during exercise training on the (measured) outcome of a cardiac rehabilitation program.

To evaluate the value of the ventilatory anaerobic threshold as outcome of cardiac rehabilitation, compared with peak VO$_2$.

**§ 1.3.3 Structure.**

In chapter 2 and 3 two important parameters of exercise capacity will be discussed, respectively the (ventilatory) anaerobic threshold and peak VO$_2$. Both will be compared on outcome of a cardiac rehabilitation program in chapter 5.

In chapter 4 the impact of mode of movement during exercise training will be discussed, when an exercise program dominated by bicycle training is compared with a program with a combination of bicycle and walking or jogging. Program evaluation will be continued in the next chapters, when the short-term effects of a high frequency program will be compared with a low frequency program on exercise capacity (chapter 5), on health related quality of life (chapter 6), and on self-efficacy in particular (chapter 7). The long-term effects of both programs will be reported in chapter 8.

A summary and conclusive remarks will be given in chapter 9, with an appendix in Dutch.
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